Rheumatic manifestations of chikungunya: emerging concepts and interventions

Andreas Suhrbier ^{1,2}

Abstract | The largest epidemic ever recorded for chikungunya, a disease caused by infection with the chikungunya virus (CHIKV), began in Africa in 2004 and spread to >100 countries on four continents. The epidemic caused >10 million cases of often debilitating rheumatic disease, classically involving rapid onset of fever and polyarthralgia, often with polyarthritis. The clinical diagnosis of chikungunya is often complicated by infections with dengue or Zika virus. For many individuals with chikungunya, the disease is benign and self-limiting; however, some patients have a complex spectrum of atypical and severe manifestations. Many patients also experience a chronic phase of the disease, primarily involving arthralgia (which can be protracted (>1 year)), and a number of sequelae are also recognized. CHIKV-induced arthropathy arises from infection of multiple cell types in the joint and the infiltration of mainly mononuclear cells. Innate responses (primarily involving type I interferon responses and natural killer cells) and cognate responses (primarily involving CD4 T helper 1 cells), alongside activation of macrophages and monocytes, mediate CHIKV-induced arthritic immunopathology. Ideally, improved anti-inflammatory treatments should not compromise antiviral immunity. New concepts in mosquito control are being field tested and a number of CHIKV vaccines are being developed.

Pandemic

An epidemic of disease that has spread across a large region; for instance, multiple continents, or even worldwide.

Attack rate

The total number of new cases of a disease divided by the total population (that is, the percentage of a defined population that is affected by a disease).

¹Inflammation Biology Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia.

²Australian Infectious Disease Research Centre, Brisbane, Queensland, Australia.

e-mail: Andreas.Suhrbier@qimrberghofer.edu.au

<https://doi.org/10.1038/s41584-019-0276-9>

Chikungunya virus (CHIKV) is a member of a group of globally distributed, mosquito-transmitted arthritogenic alphaviruses that cause sporadic outbreaks of primarily rheumatic disease every 2–50 years^{1–4}. The largest epidemic of CHIKV disease (hereafter simply referred to as chikungunya) ever recorded began on Lamu Island, Kenya, in 2004 (FIG. 1). The epidemic expanded across four continents, with cases still being reported in 2019 (FIG. 1; Supplementary Table 1). Three major genotypes of CHIKV are now recognized — the Asian, the West African and the Asian and East–Central South African (ECSA) genotypes⁵ — but a new lineage, the Indian Ocean Lineage (IOL), also emerged from the ECSA genotype during the 2004–2019 epidemic⁶. The epidemic reached >100 countries (Supplementary Table 1), caused >10 million cases (Supplementary Table 2), and might arguably be called a pandemic. An estimated 1.3 billion people are at risk of chikungunya⁷. Climate change modelling suggests that many more areas of the world (including parts of China, sub-Saharan Africa, South America and the United States) might become able to accommodate transmission of CHIKV in the future^{8,9}.

Chikungunya was previously often viewed as (and for many patients remains) a relatively benign and self-limiting rheumatic disease. However, a considerably

more complex spectrum of less common atypical and severe manifestations is now recognized in subgroups of patients, with chikungunya often complicated by comorbidities and co-infections. Hospitalization rates for chikungunya range from 0.6% to 13%^{10–14} and estimates of chikungunya-related mortality range from 0.024% to 0.7%^{10,12,15–17}. In addition, many patients develop protracted rheumatic disease lasting many months, occasionally years, with a number of sequelae now also recognized^{18–22}. Estimates for the total economic costs (direct and indirect) of chikungunya have ranged from a median of US\$67 for adults and \$258 for children in Columbia²³, to a mean of \$150 per outpatient and \$3,300 per inpatient in 2006 in Réunion Island¹¹. In a large study of a chikungunya outbreak in Bangladesh in 2017, >10 days of productivity were lost in ~30% of patients with chikungunya because of severe arthropathy²⁴. Such costs might be viewed as relatively modest by Western standards; however, the occasionally high attack rate of chikungunya, with up to 30–75% of a given population affected by chikungunya disease at any one time^{1,25}, can result in a substantial economic burden, especially in resource-poor communities that are often affected by the disease²⁶.

Considerable research in patients and animal models has now provided extensive insights into the complex

Key points

- After the 2004–2019 epidemic of chikungunya virus (CHIKV), the largest chikungunya epidemic ever recorded, this disease remains a global problem.
- New treatment options are needed for patients with chikungunya arthropathy, in particular for patients with chronic arthralgia and/or life-threatening manifestations, which primarily present in the very young and the elderly.
- The mechanisms by which CHIKV or viral material persists in joint tissues and drives chronic disease are unclear; characterizing the processes involved might open up new avenues for clinical interventions.
- Better control and evaluation measures are required to prevent transmission of arboviral diseases such as chikungunya.
- The unpredictable nature of chikungunya outbreaks complicates phase III field trials of vaccines; new solutions for trialling these vaccines are needed, which could involve human challenge models and systems vaccinology.

spectrum of disease manifestations, the important antiviral factors and the central mediators of arthritic immunopathology. These insights have led to improved disease classification and management, and have spawned a plethora of potential avenues for new interventions. This Review provides an overview of the lessons learned about chikungunya in the aftermath of the 2004–2019 epidemic. The disease manifestations are outlined, including those associated with acute, atypical acute and severe acute disease, as well as the chronic phase of the disease and its potential sequelae. Disease in infants and children, and mother-to-child transmissions, are also discussed as the clinical presentations in this group of patients differ. Also covered are comorbidities, which increase the risk of severe disease, and co-infections with Zika virus (ZIKV) and dengue virus (DENV).

Disease manifestations of chikungunya

Estimates for the asymptomatic infection rate for CHIKV range from 3% to 82%. The breadth of this range, derived from a comprehensive review of 24 studies, is similar to that found with other infectious diseases and has yet to be fully explained²⁷. Four clinical forms of symptomatic chikungunya were proposed in an expert consultation, led by the WHO–Pan American Health Organization: acute, atypical acute, severe acute and chronic (suspected or confirmed)^{28,29}. The three acute forms of chikungunya are associated with a range of different symptoms, with confirmation of diagnosis usually achieved by IgM serology (BOX 1; Supplementary Table 3). Other classifications of chikungunya have included a sub-acute phase between acute and chronic³⁰, with chronic disease defined as disease lasting >3 months^{30,31}. Generally, patients with chronic disease do eventually recover (usually within 3–24 months)^{18,19}, although sequelae might arise. An emerging body of evidence suggest that the IOL lineage is associated with more severe presentations than the Asian genotype^{19,32,33}. Infection with other arthritogenic alphaviruses can cause similar acute symptoms (such as fever, polyarthralgia–polyarthritis, rash and myalgia)¹, but rarely result in the atypical or severe manifestations that can occur with chikungunya, although such manifestations have been documented for Mayaro virus infections³⁴.

Acute chikungunya

The distinctive features of chikungunya onset are usually fever and polyarthralgia, often accompanied by polyarthritis (TABLE 1). The fever is often of rapid onset and high grade, with one large study reporting a mean maximum body temperature of 39.8°C (SD ±0.5°C) and fever duration of 4.88 days (SD ±2.7 days)²⁴. Polyarthralgia usually starts around the same time as the fever and is often incapacitating, usually symmetrical and primarily involves peripheral joints^{19,24,35,36} (FIG. 2). Acute chikungunya commonly also involves a rash, which is usually maculopapular and predominantly located on the trunk and extremities, but also occurs less frequently on the face, palms, or soles^{19,37}. The constellation of manifestations typically associated with acute disease (TABLE 1) seems to be considerably less common or less overt in older patients (>65 years of age), who have a much higher frequency of atypical or severe forms of chikungunya (as well as having a higher frequency of comorbidities) than younger patients²⁹. Hence (along with inherent variability, different diagnostic criteria and different data acquisition processes), the wide ranges in the percentages of patients with certain symptoms (for example, 10–80% for myalgia) might also reflect the age distribution of patients included in the study cohorts.

Atypical acute chikungunya

A large collection of atypical manifestations of acute chikungunya, affecting a range of systems and organs (for example, neurological, cardiovascular, skin, renal and respiratory manifestations) have been documented, often in hospital settings^{10,29,38–40} (TABLE 2). Although most patients with chikungunya admitted to hospital (~80% in one study¹⁰) do not have severe symptoms, many patients have atypical manifestations that can become severe and/or have chikungunya complicated by co-infections and/or comorbidities. Hospitalization rates for patients with chikungunya have varied from 0.6% (Martinique and Guadeloupe¹⁰), through 2.3% (Réunion Island¹¹), 3.3% (Brazil¹²) and 6% (India¹³) to 13% (Puerto Rico¹⁴). The mean length of hospital stay reported for these patients was 5 days (SD ±7 days; range 0–146 days) in Réunion Island¹¹ and 9 days (range 0–46 days) in Martinique and Guadeloupe¹⁰.

Severe acute chikungunya

CHIKV infection can result in severe manifestations, the most prevalent being cardiac or multiple organ failure^{17,38,41} (BOX 2). Chikungunya-associated viral sepsis and septic shock can also be fatal; for instance, in one study in Guadeloupe of patients with severe chikungunya, 25 out of 42 patients had septic shock, 12 of whom died⁴². Chikungunya can result in neurological complications⁴³, with mortality often associated with central nervous system (CNS) diseases including encephalitis and encephalopathy⁴⁴. Renal failure also seems to occur frequently in severe cases of chikungunya⁴⁵ and is a reported cause of death³⁸. Other rarer causes of chikungunya-related death that have been reported include toxic hepatitis, bullous dermatosis, myocarditis/pericarditis, respiratory failure, pneumonia and acute myocardial infarction³⁸. Chikungunya-related

Fig. 1 | Emergence and spread of the 2004–2019 CHIKV epidemic. In 2004, the first outbreak of the largest epidemic of chikungunya ever recorded began on Lamu Island, in Kenya (red star). The epidemic then expanded west within Africa, and also spread eastwards across islands in the Indian Ocean to Asia. The epidemic grew within India and Southeast Asia, moved east to the Pacific Islands and reached the Caribbean (Saint Martin Island) in 2013 (red diamond). Saint Martin Island was the first site in the Americas to report autochthonous transmission (completion of a human-to-mosquito-to-human transmission cycle within the same geographical location) of CHIKV. From there, CHIKV spread into Central and South America, and cases were still being reported in 2018/2019. Small outbreaks have also occurred in Europe and southern USA. Three major genotypes are recognized — West African, East–Central South African (ECSA) and Asian — suggesting at least three separate introductions of CHIKV from natural reservoirs into human populations during this epidemic. *Aedes aegypti* was the primary vector in Central and South America, most of Africa and the Pacific Islands. *Aedes albopictus* was the primary vector in Europe and parts of the Indian Ocean, West Africa and Papua New Guinea. Both vectors were likely involved in many parts of Asia.

mortality estimates vary for different regions: for example, studies have reported a mortality of 0.024% in Martinique and Guadeloupe¹⁰; 0.09% in Brazil¹⁷; 0.1% in Réunion Island¹⁶; 0.2% in India¹²; and 0.7% in the Dominican Republic¹⁵. However, the denominator for these percentages (that is, the total number of individuals with chikungunya in these regions) is often difficult to establish accurately in resource-poor settings. A mortality of 0.1%, derived from Réunion Island, might be viewed as a reliable estimate owing to the developed health care and reporting systems in this overseas region of France. Notably, old age (>40–75 years, depending on the study) is a risk factor for severe disease and mortality for individuals infected with either the Asian or IOL viruses^{15,17,30}, whereas young age (<1 year) or old age (>65 years) increased the risk of CNS disease in a study on Réunion Island⁴⁴.

Chronic disease and sequelae

Arguably the most widespread cause of morbidity in patients with chikungunya is chronic disease, although the percentage, longevity, definition, terminology and evaluation of chronic disease vary widely between studies. A meta-analysis reported that ~25% of patients with

chikungunya have had disease for >2 months and ~14% for >18 months¹⁸. Another meta-analysis of patients with chikungunya (that included patients with non-rheumatological manifestations) suggested that 43% of patients had not recovered within 3 months, and 21% had not recovered within 12 months¹⁹. However, a prospective study in India of 509 patients with chikungunya reported that all but 0.3% of the patients had recovered within 1 year⁴⁶. The primary symptoms for chronic disease in patients with chikungunya are arthralgia and/or arthritis (up to 79% of patients with chronic disease), alopecia (10–29%) and depression (6–54%)^{20,22}. Fatigue, mood disorders and sleep disorders were also common chronic symptoms¹⁹. Factors predisposing to chronic disease included comorbidities (such as osteoarthritis and diabetes), older age (>35–45 years for joint pain), and high viraemia and severe disease during the acute stage²⁰. Chronic arthralgia in chikungunya generally involves the same joints affected during the acute phase (FIG. 2) and the arthropathy is not usually overtly erosive^{16,47}.

Long-term sequelae of chikungunya include depression, chronic fatigue²² and other neurological disorders²¹. Difficulties remain in separating true sequelae from the

Viraemia

The presence of virus in the circulating blood.

Box 1 | Diagnosis of chikungunya

In 2015, a Pan American Health Organization–WHO expert consultation group provided a definition of a typical confirmed case of chikungunya. This definition can be summarized as “fever and joint pain with acute onset” and either “residing or visiting areas with local transmission of chikungunya” or “laboratory confirmation by immunoglobulin or RT-PCR”²¹². However, the primary symptoms of acute chikungunya (TABLE 1) are often shared with other co-circulating (and occasionally co-infecting) arboviruses such as Zika virus (ZIKV) or dengue virus (DENV), which can complicate the clinical diagnosis²¹³. Excluding the possibility of DENV infection in cases of suspected acute chikungunya might be critical, especially for paediatric patients with dengue who might require life-saving intravenous fluids²¹³. Some distinguishing features between chikungunya and dengue are provided by the WHO²¹⁴ and elsewhere^{2,35}. Differential diagnoses for chikungunya include other infectious or autoimmune arthritides, malaria and drug reactions¹. Commercially available diagnostic test kits for chikungunya are available (Supplementary Table 1); the tests are based on the detection of anti-CHIKV IgM antibodies (serology) or viral RNA (PCR).

progression of underlying comorbidities^{19,48}, identifying the independent development of new disease entities and/or determining when patients with chikungunya have recovered and returned to the normal community background levels of musculoskeletal disease. The prevalence of musculoskeletal disease is increasing, with disability-adjusted life-years for musculoskeletal conditions having risen by 61.6% between 1990 and 2016, and by 19.6% between 2006 and 2016. Musculoskeletal conditions include >150 diagnoses, with about a third of people worldwide living with a chronic, painful musculoskeletal condition⁴⁹. Therefore, a patient presenting with a musculoskeletal condition might be granted the same diagnostic rigour, regardless of whether or not they had a diagnosis of chikungunya >6–12 months previously.

Disease in infants and children

Both infants and children can develop chikungunya after a mosquito bite, and neonates can be infected via mother-to-child transmission (BOX 3). Infants (<1 year old) with chikungunya are often hospitalized and admitted to an intensive care unit (ICU)^{16,50}. The disease usually presents as fever and rash^{51,52}; arthralgia is difficult to assess in infants, but is perhaps expressed as irritability and excessive crying^{28,50}. Skin rashes are common (~60–80%) and generalized, and include maculopapular rash, pigment changes, vesicubullous lesions (fluid-filled lesions) and (sometimes extensive) desquamation (skin peeling)^{16,50–52}. Atypical symptoms include (sometimes complex) seizures, diarrhoea, tachycardia, viral sepsis and septic shock^{51–54}.

Acute chikungunya in children (from 1 to 18 years old) is comparable with disease in adults^{50,54,55}, although the rate of asymptomatic infection might be higher overall than in adults^{27,56}. Children (aged 2 months to 12 years) seem to generate stronger innate immune responses than adults⁵⁵, which might explain the reduced severity of arthritis and lower rates of chronic arthropathy (5–11%) in children^{50,57}. Nevertheless, a study from the 2014 epidemic in the Caribbean reported that 8.7% of children with chikungunya were hospitalized⁵⁷. Common acute atypical manifestations include vomiting and seizures⁵⁴. Severe disease primarily involves the CNS^{44,54,58}, but chikungunya can also affect multiple systems and lead to severe viral sepsis and septic shock^{53,59}.

Severe manifestations are occasionally associated with mortality^{16,50,54}.

Comorbidities and co-infections

Comorbidities

Comorbidities such as hypertension, diabetes (both type I and type II) and cardiac disease can contribute to chikungunya severity and admissions to the ICU⁶⁰. For example, diabetes can increase the severity and duration of chikungunya and in patients with diabetes and hyperglycaemia, chikungunya infection is associated with worsening of diabetic symptoms (such as poor glycaemic control and acute complications)⁶¹. The presence of comorbidities is also associated with increased morbidity. For example, in a cross-sectional study of a chikungunya outbreak in north-eastern Brazil, 1% of patients with chikungunya had chronic kidney disease (amongst other comorbidities that included diabetes, haematological disorders, liver disease, hypertension and autoimmune diseases); these patients had higher frequencies of the main acute manifestations of chikungunya and higher mortality than patients without chronic kidney disease¹². In another study of 65 patients with chikungunya who were admitted to ICUs in Martinique and Guadeloupe, 83% had pre-existing underlying comorbidities (hypertension, diabetes, renal disease, cardiac disease or autoimmune disease, including systemic lupus erythematosus) and the mortality rate among these patients was 27%⁶². Similarly, of 64 patients with chikungunya who were admitted to ICUs in French Polynesia, 77% had pre-existing conditions and 28% died⁶³. The aforementioned comorbidities also often exacerbate disease after infection with other viruses such as DENV, West Nile virus and influenza virus^{60,61}. Perhaps surprisingly, in a case series and literature review of patients with chikungunya undergoing a solid organ transplantation, most patients experienced no graft issues and a benign clinical course of chikungunya, with immunosuppressive treatment perhaps decreasing the risk of severe or chronic chikungunya immunopathological manifestations⁶⁴.

Co-infections

The symptoms, vectors and geographic distribution of the arboviruses DENV, ZIKV and CHIKV overlap considerably^{3,65,66}. All three viruses are associated with fever, arthropathy and rash, which can complicate clinical diagnoses. All these viruses are also transmitted by *Aedes aegypti* and co-circulate in parts of South America, Africa and Asia, leading to co-infections. For instance, in a cohort of patients with febrile syndrome at the Colombian–Venezuelan border, 7.64% of patients were co-infected with both DENV and CHIKV, and 1.91% were co-infected with DENV, CHIKV and ZIKV⁶⁷. Similarly, in a Nicaraguan study of patients with a suspected arboviral infection, 27% of patients tested positive for two or three of these viruses; however, the presence of DENV and/or ZIKV had no notable effects on CHIKV viraemia⁶⁸. In a study in India, 12.4% of hospitalized patients with acute symptoms of chikungunya had IgM antibodies against both CHIKV and DENV; however, the only disease exacerbation associated with

Arboviruses

Viruses that can be transmitted by arthropod vectors (for example, mosquitoes) to vertebrate hosts (for example, humans)

dual infection was diarrhoea (found in 16.2% of these patients)⁶⁹. Patients with both chikungunya and dengue were also reported to have more severe arthropathy, myalgia, thrombocytopenia and rash than patients with dengue alone⁷⁰. Such dual-infected patients were also more likely to have a rash and be hospitalized than patients with chikungunya alone⁷¹. The mortality rate is potentially higher in patients infected with both DENV and CHIKV than patients infected with either virus alone, although the evidence is weak given the very low patient numbers^{72,73}. Finally, patients with chikungunya and a preceding DENV infection are at a higher risk of developing aggravated chronic chikungunya⁷⁴. However, other studies have reported no notable exacerbation or unique presentations associated with acute dual or triple infections with the aforementioned arboviruses^{75,76}. Thus, co-infections do not reliably cause novel clinical manifestations, nor do they generally seem to require unique clinical management⁷⁷. However, patients with a potential DENV infection should not be given aspirin or other NSAIDs until they have been afebrile for ≥ 48 h and have no warning signs for severe dengue⁷⁸.

Co-infections with CHIKV and either HIV⁷⁹ or malaria have also been reported⁶⁵. In patients infected with both HIV and CHIKV, lymphopenia was more common, more patients reached the definition of severe immunosuppression, and CD4 counts were lower than in patients infected with HIV alone⁷⁹. Although the effect of CHIKV/malaria co-infections in humans remains unclear, mouse studies suggest that malaria infection can ameliorate chikungunya-related arthropathy⁸⁰. In mice, CHIKV infection can compromise lymph node function⁸¹ and alter CD8 T cell trafficking⁸², with such CHIKV-mediated changes potentially modulating adaptive immunity and thus immunopathology in co-infection settings.

Immunopathology

Antiviral versus arthritic responses

In the advent of the recent unprecedented outbreak of chikungunya (FIG. 1), our understanding of the innate and adaptive immune responses induced by CHIKV infection, both in humans and in animal models, has grown substantially^{31,83–87}. A range of cells and mediators have been implicated in chikungunya immunopathology (Supplementary Table 4). Importantly, many responses that promote chikungunya immunopathology are also required for protection against viral infections, which is clearly an important consideration in the development and application of new therapeutic interventions.

The type I interferons, primarily IFN β and subtypes of IFN α , are antiviral cytokines that mediate highly effective protection against alphavirus infection⁸⁸. These cytokines have an important function in limiting the sharp increase in viral replication during the early stages of infection^{88,89}. The anti-alphaviral activity of type I interferons is optimal at 37°C and this activity decreases with decreasing temperatures, being noticeably lower even with a reduction of only 2°C (REF.³⁶). In CHIKV-infected mice, the virus can replicate better in the extremities than elsewhere in the body because these tissues are usually a few degrees cooler, which might

explain why the peripheral joints are usually affected in alphaviral arthropathies (FIG. 2)³⁶. In the arthritic limbs of mice, up to ~8% of polyadenylated RNA can be of viral origin⁹⁰, attesting to the extraordinary replicative capacity of CHIKV in the peripheral joints at slightly reduced temperatures. However, in addition to inhibiting viral replication, type I interferons can also promote arthritis. For example, injection of polyinosinic:polycytidylic acid (a mimic of viral double-strand RNA and potent inducer of type I interferon production) into the feet of mice can induce arthritis, and recapitulates much of the inflammatory gene expression signature that occurs in mouse feet during CHIKV arthropathy³⁶.

In mice, B cells, T cells and natural killer (NK) cells are not required for survival during an acute infection⁹¹, whereas an intact type I IFN response is critical^{88,89}. Deficiencies in components of the complex type I IFN network⁸⁸ in the elderly (>65 years)^{92,93} and in neonates (<4 weeks old) might explain the increased risk of severe disease in these patient populations. For instance, neonates and very young children (<3 months) have attenuated RIG-I responses (required for the detection and triggering of type I IFN responses)⁹⁴ and neonates have impaired interferon regulatory factor (IRF) 7 activation⁹⁵ (required for amplification of the type I IFN response⁸⁹). Monocytes from elderly individuals (>65 years old) have reduced expression of TNF receptor-associated factor 3 and IRF8 (both required for optimal RIG-I signalling) compared with monocytes from younger individuals⁹². Elderly individuals can also have slightly lower body temperatures than younger individuals^{96,97}, which might also result in reduced antiviral type I interferon activity post-infection³⁶.

The clearance of viraemia requires antiviral antibodies^{85,91,98}. Neutralizing anti-CHIKV IgM responses are apparent as early as 4 days after the onset of symptoms⁹⁹ and the presence of CHIKV-specific IgG3 antibody responses 7–10 days post-onset of symptoms is associated with more severe acute disease but decreased likelihood of persistent arthralgia¹⁰⁰. CHIKV-specific CD4 T cells are required for IgG class switching and

Table 1 | Typical symptoms of acute chikungunya

Symptoms (duration)	Percentage of patients ^a	Refs
Arthralgia (weeks to months)	80–100	24,118,204–206
Arthritis (weeks to months)	62–100	24,204
Fever (usually lasts 1 week)	80–100	1,118,204
Myalgia (usually lasts ~7–10 days)	10–85	1,24,118,205,206
Headache	30–90	24,118,205,206
Rash (usually lasts ~1 week)	36–88	1,24,118,204,205,207
Fatigue	43–67	118,207
Diarrhoea	25	24,205
Oedema	22–39	24,206

^aPercentages of patients with the indicated symptoms, with the ranges encompassing all referenced studies.

IgG class switching
The switching of B cell immunoglobulin production from IgM to IgG antibodies

Efferocytosis

The process whereby dying or dead cells are removed by phagocytic cells.

efficient production of anti-CHIKV IgG antibodies⁹¹, but these cells are also major promoters of arthritic inflammation.

Finally, monocytes and macrophages also have antiviral activity against CHIKV^{101–103}, and are important for efferocytosis¹⁰⁴ and resolution of inflammation¹⁰⁵. However, as discussed in the next section, these cells are also highly implicated in chikungunya immunopathology.

A major objective for the field has been to identify appropriate pro-inflammatory mediators that can be targeted without compromising protective antiviral responses^{86,106}. TNF is induced during CHIKV infections^{90,107–109} (FIG. 3), and TNF inhibitors (including etanercept and adalimumab) have shown some promise in the treatment of patients with chikungunya¹¹⁰. However, in mice with an active infection of Ross River virus (RRV) (a close relative of CHIKV that causes RRV disease), treatment with etanercept resulted in 100% mortality, indicating that TNF also has important antiviral activities¹¹¹. This protective function of TNF against viral infections might raise concerns about TNF inhibitors for the treatment of patients with chikungunya; however,

exacerbation or reactivation of CHIKV infection is unlikely once patients have adequate levels of neutralizing antibodies. Such antibodies (detectable 4 days after the onset of disease) are clearly present in patients with a positive serodiagnosis⁹⁹ and have long been present by the time the chronic phase of disease begins¹¹². Indeed, in patients with chronic manifestations of chikungunya, treatment with an immune-modulating biologic agent (including infliximab and etanercept) was not associated with overt worsening of disease¹¹³. An important issue to consider, however, is potentially compromising antiviral immunity in settings where multiple arboviruses are circulating. In such scenarios, therapies that target chikungunya immunopathology should ideally not compromise the patients' ability to generate immunity to subsequent DENV or ZIKV infections.

In addition to the inhibition of antiviral activity, another potential concern of anti-inflammatory interventions is the risk of inadvertently promoting immunopathology. For instance, the chemokine CC-chemokine ligand 2 (CCL2) is strongly induced during CHIKV infections^{108,109} and targeting the CC-chemokine

a Acute chikungunya

b Chronic chikungunya

Fig. 2 | **Joints affected by chikungunya arthralgia.** **a** | Joints with arthralgia at or near the time of disease onset, indicating the range of percentages of patients reporting arthralgia in each indicated joint or group of joints in previous studies of patients with acute chikungunya on Réunion Island¹⁹⁹, on Sint Maarten in the Caribbean²⁰⁰ or in India²⁰¹. **b** | Joints with arthralgia in patients with chronic chikungunya, based on data from patients with chronic chikungunya on Réunion Island²⁰², on Sint Maarten in the Caribbean²⁰⁰ or in Brazil²⁰³. Assessment methodologies were not standardized in these studies, and so it is difficult to attribute any differences across these studies to CHIKV genotypes or specific populations.

Table 2 | Atypical symptoms of acute chikungunya

Systems/organs affected	Percentage of hospitalized patients ¹⁰	Manifestation examples	Refs
Neurological	40	Encephalitis Meningoencephalitis Guillain–Barre syndrome	38–41,43
Cardiovascular	27	Hypotension Myocarditis Arrhythmias	38–41
Skin	10	Hyperpigmentation Bullous dermatosis Erythema	38–41
Renal	26	Albuminuria Haematuria Nephritis	39,40,45
Respiratory	14–26	Dyspnoea Respiratory failure Pneumonia	38,39,41
Vascular	10	Haemorrhagic signs Bleeding gums Melena	39,41,205,208,209
Ocular	Less common than other atypical symptoms	Conjunctivitis Photophobia Retinitis	39,41,210,211
Liver	Less common than other atypical symptoms	Hepatitis Hepatomegaly Altered function	38,40,41

Atypical acute manifestations can accompany the typical acute symptoms (TABLE 1). Atypical manifestations are grouped by the systems/organs affected, with some examples of manifestations provided; these are neither complete nor ranked and the reader is directed to the accompanying references for a full description of manifestations.

receptor 2 (CCR2)–CCL2 axis in mice reduces the recruitment of inflammatory monocytes and macrophages into the joints¹⁰⁴. However, in the absence of monocytes and macrophages, neutrophils are instead recruited into the joints of CCR2^{−/−} mice post-CHIKV infection, promoting joint destruction¹⁰⁴.

Mechanisms of immunopathology

Taking synovial biopsies or aspirates from patients with alphavirus-induced arthritis is often difficult to justify, as such procedures carry a small risk for the patient and usually have a negligible effect on disease management. Nevertheless, a small number of studies have analysed such material from patients with chikungunya or RRV disease^{112,114–116}. As with other viral and bacterial arthritides¹¹⁷, CHIKV-related and RRV-related arthropathies probably arise from innate and adaptive immune responses stimulated by viral material in joint tissues^{1,90,91,109,118} (FIG. 3).

The ability of CHIKV to affect multiple systems/organs might be because of the virus's predilection for infecting fibroblasts^{47,119}, a cell type that is present in many tissues and organs (including the connective tissue, skin, synovium and periosteum^{89,119}). The

widespread expression of the arthritogenic alphavirus receptor, matrix remodelling-associated protein 8 (MXRA8), also probably contributes as this receptor permits infection of a large range of different cell types¹²⁰. These cell types include circulating monocytes¹⁰⁸, macrophages¹⁰⁹, endothelial cells^{89,109}, cells of the nervous system^{43,91} and skeletal muscle cells^{47,89}, as well as cell types present in joints (FIG. 3). Infection usually induces cell death¹²¹, mainly by apoptosis^{104,106} but also to a lesser extent by necroptosis and pyroptosis¹²². Cell death might directly contribute to pathology, especially for neurological manifestations^{91,122,123}. However, immunopathology probably has the major role in the majority of rheumatic manifestations (FIG. 3, Supplementary Table 4).

Macrophages and monocytes. Arthritic infiltrates in patients with alphavirus-associated arthritides predominantly comprise mononuclear cells, mostly consisting of monocytes and macrophages but also including T cells, B cells and NK cells. In contrast to autoimmune arthritides, neutrophils are uncommon in the synovial infiltrates of patients with alphaviral arthritides^{101,112,114–116,124}. Monocytes and macrophages are strongly implicated in chikungunya arthritic immunopathology

Synovial macrophages from patients with chikungunya have an activated morphology, with a ballooned appearance and multiple vacuoles^{112,116}, indicative of a phagocytic (activated) phenotype^{108,125}. Cytokines induced during CHIKV infection, such as type I interferons, IFN γ and TNF, are well-known activators of monocytes and macrophages (FIG. 3). Studies in non-human primates suggest that macrophages are the likely site of the persistence of CHIKV and CHIKV material¹⁰⁹. Alphaviral RNA and/or proteins have also been detected in the synovial macrophages of patients with chikungunya and RRV disease^{112,114}. In vitro work in RAW264 cells (a murine macrophage cell line) suggests that CHIKV-infected macrophages are a source of arthritogenic cytokines such as TNF and IL-6¹²⁶. Mouse models of chikungunya arthritis and analysis of peripheral blood mononuclear cells from patients have also suggested a function for the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome (and thus IL-1 β and IL-18) in chikungunya, with a small-molecule inhibitor of NLRP3 activation able to reduce CHIKV-induced inflammation in mice¹²⁷. Notably, NLRP3 is also implicated in the pathogenesis of rheumatoid arthritis (RA), with high levels of NLRP3 activation being reported in monocytes/macrophages infiltrating the synovia of patients with RA¹²⁸.

As well as synovial macrophages, whole-blood RNA transcriptomic analyses in paediatric patients suggest that CHIKV infects peripheral blood monocytes (and dendritic cells) and that CHIKV induces a monocyte-centric pro-inflammatory response¹⁰⁸. CCL2 is a major product of CHIKV-infected monocytes¹²⁹, is strongly induced during CHIKV infection^{101,109} and is important for the recruitment of monocyte and macrophages into the inflamed joint¹⁰⁴. CHIKV-infected monocytes also produce other pro-inflammatory mediators, including IFN α , IL-12 and CXC-chemokine ligand 10 (CXCL10)¹³⁰ (FIG. 3).

Overall, monocytes and macrophages have a very large number of functions and differentiation states¹³¹ and interact with CHIKV on a range of levels; not only are these cells the sites of infection and persistence and the source of pro-inflammatory cytokines, these cells also have antiviral activity and are required for the resolution of inflammation.

CD4 T cells. CHIKV-specific CD4 T cells have been repeatedly implicated as important promoters of CHIKV-mediated arthritis^{80,132–136}. Furthermore, regulatory T cells can ameliorate chikungunya arthropathy in mice¹³⁷ and are also associated with disease resolution in humans¹³⁴. In mouse models of chikungunya, CD4 T cells infiltrated into the joints in a CXC-chemokine receptor 3 (CXCR3)-dependent fashion⁸⁰, with arthritogenic CD4 T cells seeming to have a dominant type 1 T helper (T_H1) cell phenotype¹³⁵, expressing the transcription factor T-bet¹⁰⁴ and IFN γ ^{32,90,101}. Notably, IFN γ -expressing cells are also present in synovial biopsy samples from patients with RRV disease¹¹⁴. Curiously, IFN γ deficiency has no major effects on mouse models of chikungunya^{90,138}. IFN γ expression was also not detectable in the synovial fluid of one patient with chronic chikungunya, although IFN γ was abundant in their blood during the acute disease phase¹¹². The contribution of IFN γ in chikungunya thus remains unclear, although it should be noted that IFN γ is reported to have a complex and pleiotropic function in RA^{139,140}.

More studies are required to better understand the mechanisms whereby CHIKV-specific CD4 T cells drive arthropathy. Conceivably, rather than being reliant on IFN γ , CHIKV-specific T_H1 cells could activate monocytes and macrophages via interactions involving CD28 and CD80–CD86^{136,141}, resulting in TNF and IL-6 production¹⁴². Alternatively, instead of IFN γ expression by T_H1 cells, TNF expression by CD4 cells might have an important function in promoting chikungunya arthropathy¹³⁵. TNF-expressing CD4 cells have a potential pathogenic function in psoriatic arthritis¹⁴³ and are targeted by methotrexate in RA^{144,145}; notably, methotrexate has shown some benefit in treating chikungunya^{146,147}.

Some animal models^{104,109,148} have suggested the involvement of IL-17 and T_H17 cells in alphaviral arthritides. Concentrations of IL-17 are marginally increased

in the plasma of patients with chikungunya during the acute phase of disease compared with that of uninfected individuals¹⁴⁹ and remain increased during the chronic phase¹⁵⁰. By contrast, IL-17 is not increased in the blood of young patients with chikungunya¹⁰⁸, who are known to experience less severe arthropathy than older patients. IL-17 is implicated in cartilage destruction and bone erosion in RA¹⁵¹, whereas radiographically detectable joint damage is not generally a feature of alphaviral arthropathy. Nevertheless, some patients with RRV disease have an increased receptor activator of nuclear factor kappa-B ligand (RANKL) to osteoprotegerin (OPG) ratio, indicative of increased osteoclastogenesis and bone resorption¹⁴⁸. The levels of matrix metalloproteinase 2 (MMP2) messenger RNA were increased in the synovial fluid of one patient with chronic chikungunya (compared with levels in healthy individuals)¹¹². Furthermore, concentrations of connective tissue metabolites (proline, hydroxyproline and mucopolysaccharides) were increased in the urine of patients with chikungunya during the first week post-onset of fever¹⁵². Thus, although alphaviral arthritides might be associated with some IL-17 production, cartilage destruction and bone erosion, the contribution of these processes to alphaviral rheumatic pathology seems to be substantially less important than their role in RA.

NK cells and NK T cells. Synovial NK cells (characterized by their CD56⁺ CD3[−] expression) in patients with chronic chikungunya express the activation marker CD69¹¹², and data from mouse models suggest that NK cells have a pathogenic role in acute arthropathy^{32,90,91}. NK cells from the peripheral blood of patients with acute chikungunya have an activated profile (including the expression of the heterodimer CD94:NKG2C) and are strongly cytotoxic, but secrete minimal levels of IFN γ ¹⁵³. NK cells in the peripheral blood of patients with chronic chikungunya express reduced levels of perforin, but they do not express notably higher levels of TNF or IFN γ compared with NK cells from healthy individuals¹⁰⁷. Increased numbers of synovial CD56⁺ NK cells in patients with established RA probably promotes arthritis via secretion of TNF and IFN γ ¹⁵⁴; however, the mechanisms by which NK cells contribute to chikungunya arthropathy remain to be elucidated⁹⁰.

In addition to NK cells, natural killer T (NKT) cells (characterized by their CD56⁺ and CD3⁺ expression) that express TNF or IFN γ are increased in the peripheral blood of patients with chronic chikungunya compared with healthy individuals, and are similarly increased in patients with RA compared with healthy individuals¹⁰⁷. Hence, NKT cells are likely to contribute to both chikungunya and RA arthropathy, but the underlying mechanisms and their importance remain unclear.

Non-haematopoietic cells. Fibroblasts in connective tissues are a major target of CHIKV infection and produce various IFN α subtypes and IFN β ¹¹⁹, cytokines with well-described arthritogenic properties³⁶. In vitro, CHIKV-infected human synovial fibroblasts secrete RANKL, IL-6, IL-8 and CCL2, and supernatants from these cultures can stimulate osteoclastogenesis^{155,156}.

Box 2 | Severe symptoms of acute chikungunya

Severe symptoms of acute chikungunya (listed below) are defined as manifestations that include dysfunctions of at least one organ or system that threatens life and requires hospitalization. The term “failure” reflects a spectrum that includes non-lethal manifestations with recovery.

- Cardiac failure^{17,38,41,42}
- Multiple organ failure^{17,38}
- Viral sepsis and/or septic shock⁴²
- Renal failure^{10,17,38,42,45}
- Liver failure^{10,17,38,42}
- Respiratory failure^{10,17,38,42}
- Encephalitis or meningoencephalitis^{17,38,42,43}
- Bullous dermatosis^{17,38}

Box 3 | Mother-to-child infections

Mother-to-child transmission usually occurs during birth and occurs in about half of viraemic (and symptomatic) mothers^{215,216}. Of the infected neonates, ~50% develop disease within 3–7 days and 2.8% of cases result in fatality²¹⁵. In a study of mother-to-child transmissions in Réunion Island, 21% of the infected neonates had persisting disabilities²¹⁷. Symptoms vary widely and include fever, poor feeding, irritability (hyperalgesia), respiratory distress, diffuse limb oedema, rashes, sepsis-like illness, meningoencephalitis and other central nervous system abnormalities, and haemorrhagic and cardiac manifestations^{215,218–220}. Neurodevelopmental delays can also occur, with one study reporting that >50% of previously symptomatic neonates had a global neurodevelopmental delay at 2 years compared with 15% of uninfected children²²⁰.

A clinical trial was planned in 2014 to evaluate treatment of infected neonates with hyperimmune human anti-CHIKV immunoglobulins to suppress infection, although no results have been posted to date²²¹. Another potential treatment, yet to be formally tested, is the use of tocolytic drugs to delay delivery of the baby by a few days, thereby allowing maternal antibodies to resolve the viraemia prior to the onset of labour^{215,217}. Tocolytic therapy is used to delay or prevent pre-term delivery²²², and is generally not recommended after 34 weeks of gestation²²³. Nevertheless, encouraging data have been reported for the use of tocolytics to delay birth in mothers with a DENV infection²²⁴, although further studies are required to establish the safety and efficacy of this approach in chikungunya.

Zika virus (ZIKV) recently caused international concern owing to its association with congenital Zika syndrome (CZS), which describes a pattern of birth defects (including microcephaly) caused by infection during pregnancy. The largest outbreak of CZS occurred in Brazil (2014–2016) and the postulated reasons for the unprecedented outbreak have been varied and remain controversial. The results of one epidemiological analysis in 2018 led the investigators to speculate that CHIKV infection might somehow increase ZIKV severity⁶⁶. CHIKV infections are not usually associated with congenital abnormalities, although the development of microcephaly after birth in CHIKV-infected neonates has been reported^{220,225}. Rare cases of placental and transplacental CHIKV infection have also been reported, and resulted in abortion²²⁶.

CHIKV can infect human osteoblasts in vitro, which promotes IL-6 and RANKL secretion by these cells and inhibits OPG secretion (increasing the RANKL to OPG ratio)¹⁵⁷. Notably, the RANKL to OPG ratio is increased in the synovial fluid of patients with RRV disease compared with synovial fluid from healthy controls, and treatment with an anti-IL-6 antibody can reduce bone loss in a mouse model of RRV infection¹⁵⁸. In addition to osteoblasts, CHIKV can also infect human chondrocytes in vitro¹²⁰ and mouse chondrocytes in vivo^{89,159}. RRV infection of chondrocytes induces the secretion of IL-6, CCL2, IFN γ and TNF α ¹⁶⁰. Thus, multiple non-haematopoietic cell types in the joint can be infected with CHIKV and might contribute to the pro-inflammatory milieu (FIG. 3).

Human skeletal muscle cells (in vitro)¹²⁰ and mouse skeletal muscle cells can also be infected by CHIKV in vivo⁸⁹, although some evidence suggests that, in humans, only skeletal muscle progenitor (satellite) cells are infected¹⁶¹. Infection of skeletal muscle might be responsible for myalgia in patients with chikungunya (TABLE 1); notably, studies of mouse models of chikungunya have reported pronounced inflammatory infiltrates in skeletal muscle tissues^{101,111}.

Chronic arthropathy

The underlying inflammatory stimuli responsible for chronic chikungunya arthropathy remain unclear^{20,47}. The persistence of the virus or viral material^{112,114,117}, as well as host cell debris¹⁶², in joint tissues probably

have important contributions. RNA-seq transcriptional profiling data from mice suggest that chronic inflammation in chikungunya is simply a prolongation of the acute inflammatory response⁹⁰, which continues until the viral material is cleared⁹¹. The expression of a number of pro-inflammatory cytokines and chemokines in the peripheral blood are associated with chronic disease in patients with chikungunya^{46,83,118} (Supplementary Table 4). Notably, the expression of pro-inflammatory mediators IL-6, IL-8, CCL2 and IFN α were upregulated in the synovial fluid of a patient with chronic chikungunya compared with expression in serum from the same patient¹¹².

In chikungunya, the virus and/or viral material seem primarily to persist in monocytes and macrophages in the joints^{109,112}, which is a feature common to a number of arthritogenic viruses and bacteria in humans and animals^{117,163}. Virus-induced apoptosis and reinfection of cells via apoptotic blebs is one postulated mechanism by which alphaviral infection might persist in vivo in the presence of neutralizing antibodies^{125,164}. However, although viral material (RNA and/or protein) can be detected, researchers have been unable to isolate infectious (replication competent) virus from the joint tissues of patients with subacute or chronic disease^{112,114,116} or from mice 2 weeks after CHIKV infection⁹¹. A number of possibilities could explain this apparent discrepancy: levels of infectious virus might simply be too low to be isolated; defective viral RNA could continue to replicate as replicons without being able to produce infectious (replication-competent) virus¹⁶⁵, with viral proteins being translated from replicon RNA, and/or residual inactive viral material is only slowly cleared⁹¹, with large amounts accumulating during the acute infection⁹⁰.

Although CHIKV arthropathy shares many features with RA^{37,83,118,132}, there is no clear evidence that autoimmune disease is involved or induced. However, viral material could not be found in synovial fluid from 38 patients with arthropathy at 22 months post-onset of chikungunya, perhaps arguing that arthropathy at this stage is no longer attributable to viral persistence and that alternative mechanisms are in play¹⁶⁶. The investigators suggested that (as yet undefined) autoimmune sequelae might be responsible (although levels of cytokines or chemokines were not assessed in this study)¹⁶⁶.

Arthralgia is a dominant feature of acute chikungunya and the main symptom of chronic chikungunya (FIG. 2). Alphaviral arthralgia probably involves inflammatory pain, perhaps driven by inflammatory cytokines; however, the mechanisms involved in both inflammatory pain in general¹⁶⁷ and in alphaviral arthralgia specifically remain poorly understood. One might speculate that IL-6 has a role in driving alphaviral arthralgia, as this cytokine features prominently in acute and chronic chikungunya^{46,112} (FIG. 3) and anti-IL-6 drugs seem effective in treating pain and fatigue in RA¹⁶⁸. Chikungunya arthralgia can also have neuropathic characteristics^{169,170}, which might involve infection and disruption of cells of the peripheral nervous system^{21,43,91}. Further research is needed to unravel the mechanisms that underpin

Replicons

Viral RNAs that can self-replicate as they encode genes required for viral RNA replication (including RNA-dependent RNA polymerase), but that are unable to form an infectious virus because of defects in, or loss of, one or more structural genes required for virus particle assembly.

Fig. 3 | Potential mechanisms of arthritic immunopathology in chikungunya. Cells and mediators thought to be involved in chikungunya arthropathy (derived from *in vivo*, *in vitro*, animal and human studies). Chondrocyte involvement is based on Ross River virus studies. CHIKV probably infects a range of cell types in the joints, resulting in the secretion of multiple pro-inflammatory mediators. Type I interferons (IFN α and IFN β) are produced, but antiviral activity is probably compromised by the lower temperatures in peripheral joints. Type 1 T helper (T_H1) cell recruitment probably involves CXC-chemokine receptor 3 (CXCR3; a receptor for CXC-chemokine ligand 10 (CXCL10)), and IL-12 and type 1 interferons are known to drive T_H1 cell polarization (activation of CD4 T cells such as T_H1 cells usually occurs via T cell receptor (TCR) engagement). CC-chemokine ligand 2 (CCL2) and CXCL10 recruit monocytes and macrophages, and

CXCL10 can also recruit natural killer (NK) cells. NK cells express the activation marker CD69 and probably contribute to arthropathy, but the mechanisms involved remain unclear. Macrophages are activated by a number of cytokines and might also be activated via CD28 and CD80/86. T_H1 cells drive arthropathy, although their secretion of IFN γ is largely dispensable for this activity. IL-17 and T_H17 cells might have a role, although neutrophils are usually absent. Osteoblast and chondrocyte infection and osteoclastogenesis might result in some joint damage, although this joint damage is not generally radiologically detectable. NKT cell, natural killer T cell; NLRP3, NOD-, LRR- and pyrin domain-containing 3; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor κ -B ligand; RANTES, regulated on activation, normal T cell expressed and secreted.

Box 4 | Mosquito control measures

Non-human primates are believed to be the major reservoir for chikungunya virus (CHIKV), and the virus is transferred via mosquito vectors (mainly the forest or savannah *Aedes* species). Occasional introduction of the virus into urban areas initiates sporadic outbreaks that involve human-to-mosquito-to-human transmission cycles⁴⁰. *Aedes aegypti* was traditionally the primary vector, and remains an important vector for CHIKV. However, in the 2004–2019 epidemic, Indian Ocean Lineage isolates emerged that, compared with other strains, had an increased capacity to be transmitted by *Aedes albopictus* owing to a mutation in the surface glycoprotein (E2, A226V) of CHIKV (although other mutations might also be involved)²²⁷. *Aedes albopictus* is an aggressive biter with an ever-increasing global distribution²²⁸ and tends to bite humans outdoors during the day or early evening; thus, CHIKV transmission is minimally affected by bed nets²²⁹. Air-conditioned premises tend to have low mosquito numbers (as windows are usually closed), but the expense of this equipment precludes its widespread use in poor communities²³⁰. Use of mosquito repellent is often limited, even after media campaigns and distribution of free repellent²³⁰. Use of insecticides in public health settings remains the cornerstone of control efforts; however, whether this approach is actually effective against *Aedes* and associated arboviral diseases is unclear²³¹. The global growth of insecticide resistance also further compromises control measures²²⁹. Alternative control strategies are being developed, such as introducing an insect toxin into a fungus that infects mosquitoes²³². Another advanced example uses *Wolbachia* (a Gram-negative bacteria that infects mosquitoes), with a large field trial of *Wolbachia*-infected *A. aegypti* currently underway in Yogyakarta, Indonesia, with the hope that transmission of DENV, ZIKV and CHIKV can be reduced²³³. The approach has already had promising results in reducing cases of dengue in Townsville, Australia²³⁴.

alphaviral arthralgia, with such endeavours hopefully leading to new therapeutic approaches.

Treatments and vaccines

Anti-inflammatory therapy

A number of consensus guidelines^{30,146,171}, reviews^{2,35,113,172–174} and perspectives^{37,175} for the treatment and management of chikungunya are available. In summary, acetaminophen (paracetamol) is recommended for the initial treatment of fever and pain. If pain-relief is inadequate, NSAIDs are the mainstay of treatment (except in patients with a suspected DENV infection⁷⁸). However, NSAIDs are contraindicated in several comorbidities, including uncontrolled hypertension, kidney disease and inflammatory bowel disease, and NSAIDs should be discontinued in pregnant patients 6–8 weeks before birth. Low-dose corticosteroids (with or without NSAIDs) seem to be effective in NSAID-refractory patients^{35,113,146,171,175}, although the potential adverse effects of these drugs should be considered in risk-benefit assessments^{31,176}. For patients with chronic chikungunya who are refractory to the aforementioned treatments, DMARDs have shown some efficacy^{113,172}, and sulfasalazine and methotrexate have been suggested as first-line options^{146,147}. However, chikungunya arthropathy is usually not overtly erosive^{16,47}, and so DMARDs might seem hard to justify¹⁷⁷ unless an underlying destructive autoimmune disease is present. Methotrexate treatment, in particular, can have rare but potentially serious adverse effects and requires extensive clinical monitoring. Another DMARD, chloroquine, has also been reported to worsen disease¹⁷⁸.

Targeting pathogenic CD4 T cells has shown some promise in animal models of chikungunya. For example, treatment with abatacept, a CTLA4-Ig fusion protein that interferes with T cell activation, ameliorated

chikungunya in mice without affecting viraemia; however, this therapy was only partially effective unless combined with an antiviral antibody¹³⁶. Although biologic drugs are an exciting new avenue for targeting specific arthritic pathways, the high cost of these drugs might preclude their widespread use, especially in resource-poor settings. Human data for the use of biologics in the treatment of chikungunya are also currently limited, inconclusive and/or complicated by autoimmune comorbidities^{113,172}. Finally, fingolimod (a sphingosine 1-phosphate receptor agonist that is used to treat relapsing forms of multiple sclerosis¹⁷⁹) has also shown preliminary potential for treating chikungunya. Treatment with this agonist, which sequesters lymphocytes in lymph nodes to prevent their participation in tissue inflammation, was able to abrogate chikungunya in a mouse model¹³³; however, the cost of this drug might limit enthusiasm for this treatment in humans, especially in resource-poor settings.

Antiviral treatments

There has been substantial preclinical evaluation of antiviral chemotherapeutic drugs for inhibiting CHIKV infection, which will not be reviewed herein as few of these drugs have been tested in vivo and none has reached or shown efficacy in human clinical trials. Whether an antiviral approach seeking to inhibit viral replication would be effective against CHIKV is unclear. In most patients, by the time a diagnosis has been reached and treatment has been initiated, virus and/or viral RNA replication could be largely over. Conceivably, low-level RNA replication (evidence of which is currently lacking in patients) might drive chronic disease and could thus be targeted by antiviral drugs.

Antiviral monoclonal antibody treatments have also shown promise in mouse models^{103,180,181}. However, by the time a serodiagnosis of chikungunya is obtained (BOX 1), patients usually already have antiviral antibodies, and chronic disease occurs despite ongoing robust antibody responses¹¹². The settings and window of opportunity wherein such antibody treatments might be effective might thus be quite limited¹³³, and the high cost of such antibodies will probably limit their widespread use.

Vaccine development

As well as treatment strategies, disease prevention measures (such as vaccines and mosquito control measures (BOX 4)) are in development. CHIKV vaccines most often use the structural polyprotein of CHIKV; this polyprotein is cleaved into five proteins (E1 and E2 viral spike glycoproteins, capsid, E3 and 6 K) that assemble into a viral particle, thereby presenting an authentically folded quaternary structure to the immune system^{182,183}. Vaccination seeks to recapitulate naturally acquired protective immunity (generated after infection with CHIKV) and induce neutralizing antibodies directed at the viral spike glycoproteins (comprising E1/E2 trimers). Such antibodies are thought to be the main mediators of protection⁹⁸ by blocking the virus from binding to the receptor¹²⁰, by blocking viral entry into cells and/or by preventing viral budding^{180,184}.

Virus-like-particle vaccine
A protein-based vaccine that recapitulates the appearance and structure of a virus particle, but that has no capacity to replicate in the vaccine recipient because, for instance, the viral genome is (in part or wholly) missing.

Human challenge model
In a CHIKV vaccine context, volunteers are vaccinated with a CHIKV vaccine and are then infected with CHIKV (likely an attenuated CHIKV for safety reasons) in a controlled hospital setting (distinct from conventional phase III trials where vaccine recipients are released into the community and can acquire CHIKV naturally).

Systems vaccinology

A systems-based approach in which transcriptional profiling (followed by bioinformatic analyses) is used to obtain a detailed picture of changes in gene expression following vaccination.

Systems serology

A systems-based approach that measures biophysical and functional characteristics of antigen-specific antibody responses (for example, responses to vaccination); measured characteristics include immunoglobulin isotypes, Fc receptor binding profiles, antibody glycosylation patterns and antibody affinity.

Serogroup

For viruses, a serogroup means that viral infection with one member of that serogroup will generate antibodies capable of recognizing (cross-reacting with) other members of that serogroup.

The global market value for a CHIKV vaccine has been estimated to be ~€500 million (~US\$ 600 million) annually; however, this value might be viewed as relatively low compared with other projects (for instance, the global influenza vaccine market value in 2018 was estimated to reach >US\$ 5 billion)¹⁸⁵. In a workshop in India in 2018, the Coalition for Epidemic Preparedness Innovations (CEPI) reported that four vaccines are in phase I human clinical trials and two vaccines are in phase II clinical trials¹⁸⁶; the latter being a recombinant measles virus vaccine that encodes the CHIKV structural polyprotein¹⁸⁷ and a virus-like-particle vaccine¹⁸⁸. Unfortunately, phase III field trials for epidemic diseases such as CHIKV are complicated by the inability to predict the geographical location and size of the next outbreak¹⁸⁹. An alternative or complementary approach to phase III field trials might involve a human challenge model (as described for dengue¹⁹⁰), in which, for instance, vaccine recipients might be challenged with a live attenuated CHIKV¹⁹¹. Such studies might be combined with systems vaccinology and systems serology approaches, which should help to provide more sophisticated correlates of protection^{192,193}.

All CHIKV genotypes seem to belong to a single serogroup^{194,195}. However, variations in cross-neutralization capacities have been reported, such that antibodies raised to one CHIKV genotype are relatively less efficient at neutralizing a different CHIKV genotype^{33,196}. Vaccines currently in development use CHIKV antigens from one CHIKV genotype; whether such (single valent) vaccines will provide broadly comparable protection against all CHIKV genotypes thus remains to be established. Another challenge will be timely deployment in rapidly evolving outbreaks; for example, during the Réunion Island outbreak, the number of infected

individuals began to escalate at the beginning of 2006, but the epidemic was largely over by July 2006¹⁹⁷.

Conclusions

The unprecedented 2004–2019 CHIKV epidemic has resulted in a surge of research into chikungunya, and has led to many new insights and consensus guidelines for clinical management. There is a clear need for better treatment options for patients with chikungunya and NSAID-refractory arthropathy, chronic arthralgia or severe, life-threatening disease. Well underway are preclinical and clinical investigations of new drugs, and drugs developed for other inflammatory arthritides (such as RA), for treating chikungunya arthropathy. Such endeavours should also facilitate treatment of arthritic disease caused by other alphaviruses such as Mayaro virus and RRV, which have the potential to cause alphavirus outbreaks^{34,198}. However, expensive treatments are unlikely to be widely adopted in resource-poor communities and in high-attack-rate settings. Protracted chronic chikungunya (particularly chronic arthralgia) remains poorly understood and complicated by comorbidities and high background levels of musculoskeletal pain in the community. Mosquito control measures are hampered by insecticide resistance and the difficulties in judging whether interventions actually effect disease prevalence. Some vaccines are in advanced stages of development; however, the limited market size does not provide a clear financial incentive for the development of vaccines, and outbreaks are unpredictable. New agencies (such as the CEPI) and technologies are probably needed to bring such interventions to the market¹⁹³.

Published online 3 September 2019

- Suhrbier, A., Jaffar-Bandjee, M. C. & Gasque, P. Arthritogenic alphaviruses – an overview. *Nat. Rev. Rheumatol.* **8**, 420–429 (2012).
- Silva, J. V. J., Jr. et al. A scoping review of Chikungunya virus infection: epidemiology, clinical characteristics, viral co-circulation complications, and control. *Acta Trop.* **188**, 213–224 (2018).
- Weaver, S. C., Charlier, C., Vasilakis, N. & Lecuit, M. Zika, chikungunya, and other emerging vector-borne viral diseases. *Annu. Rev. Med.* **69**, 395–408 (2018).
- Burt, F. J. et al. Chikungunya virus: an update on the biology and pathogenesis of this emerging pathogen. *Lancet Infect. Dis.* **17**, e107–e117 (2017).
- Pyke, A. T., Moore, P. R. & McMahon, J. New insights into chikungunya virus emergence and spread from Southeast Asia. *Emerg. Microbes Infect.* **7**, 26 (2018).
- Weaver, S. C. & Forrester, N. L. Chikungunya: evolutionary history and recent epidemic spread. *Antiviral Res.* **120**, 32–39 (2015).
- Nsoesie, E. O. et al. Global distribution and environmental suitability for chikungunya virus, 1952 to 2015. *Euro. Surveill.* **21**, 30234 (2016).
- Tjaden, N. B. et al. Modelling the effects of global climate change on Chikungunya transmission in the 21st century. *Sci. Rep.* **7**, 3813 (2017).
- Leta, S. et al. Global risk mapping for major diseases transmitted by *Aedes aegypti* and *Aedes albopictus*. *Int. J. Infect. Dis.* **67**, 25–35 (2018).
- Dorleans, F. et al. Outbreak of chikungunya in the French Caribbean islands of Martinique and Guadeloupe: findings from a hospital-based surveillance system (2013–2015). *Am. J. Trop. Med. Hyg.* **98**, 1819–1825 (2018).
- Soumahoro, M. K. et al. The Chikungunya epidemic on La Réunion Island in 2005–2006: a cost-of-illness study. *PLOS Negl. Trop. Dis.* **5**, e1197 (2011).
- Silva Junior, G. B. D., Pinto, J. R., Mota, R. M. S., Pires Neto, R. D. J. & Daher, E. F. Impact of chronic kidney disease on chikungunya virus infection clinical manifestations and outcome: highlights during an outbreak in northeast of Brazil. *Am. J. Trop. Med. Hyg.* **99**, 1327–1330 (2018).
- Puwara, T., Shetha, J. K., Kohlib, V. & Yadav, R. Prevalence of chikungunya in the city of Ahmedabad, India, during the 2006 outbreak: a community-based study. *Dengue Bull.* **34**, 40–45 (2010).
- Sharp, T. M. et al. Chikungunya cases identified through passive surveillance and household investigations – Puerto Rico, May 5–August 12, 2014. *MMWR Morb. Mortal Wkly. Rep.* **63**, 1121–1128 (2014).
- Freitas, A. R. R., Alarcon-Elbal, P. M., Paulino-Ramirez, R. & Donalisio, M. R. Excess mortality profile during the Asian genotype chikungunya epidemic in the Dominican Republic, 2014. *Trans. R. Soc. Trop. Med. Hyg.* **112**, 443–449 (2018).
- Jaffar-Bandjee, M. C. et al. Emergence and clinical insights into the pathology of Chikungunya virus infection. *Expert Rev. Anti Infect. Ther.* **8**, 987–996 (2010).
- Brito, C. A. A. Alert: Severe cases and deaths associated with Chikungunya in Brazil. *Rev. Soc. Bras. Med. Trop.* **50**, 585–589 (2017).
- Rodriguez-Morales, A. J., Cardona-Ospina, J. A., Fernanda Urbano-Garzon, S. & Sebastian Hurtado-Zapata, J. Prevalence of post-chikungunya infection chronic inflammatory arthritis: a systematic review and meta-analysis. *Arthritis Care Res.* **68**, 1849–1858 (2016).
- Paixao, E. S. et al. Chikungunya chronic disease: a systematic review and meta-analysis. *Trans. R. Soc. Trop. Med. Hyg.* **112**, 301–316 (2018).
- van Aalst, M., Nelen, C. M., Goorhuis, A., Stijns, C. & Grobusch, M. P. Long-term sequelae of chikungunya virus disease: a systematic review. *Travel Med. Infect. Dis.* **15**, 8–22 (2017).
- Brizzi, K. Neurologic manifestation of chikungunya virus. *Curr. Infect. Dis. Rep.* **19**, 6 (2017).
- Duvignaud, A. et al. Rheumatism and chronic fatigue, the two facets of post-chikungunya disease: the TELECHIK cohort study on Réunion island. *Epidemiol. Infect.* **146**, 633–641 (2018).
- Alvis-Zakzuk, N. J. et al. Economic costs of chikungunya virus in Colombia. *Value Health Reg. Issues* **17**, 32–37 (2018).
- Hossain, M. S. et al. Chikungunya outbreak (2017) in Bangladesh: clinical profile, economic impact and quality of life during the acute phase of the disease. *PLOS Negl. Trop. Dis.* **12**, e0006561 (2018).
- Hennessey, M. J. et al. Seroprevalence and symptomatic attack rate of chikungunya virus infection, United States Virgin Islands, 2014–2015. *Am. J. Trop. Med. Hyg.* **99**, 1321–1326 (2018).
- Bonifay, T. et al. Poverty and arbovirus outbreaks: when chikungunya virus hits more precarious populations than dengue virus in French Guiana. *Open Forum Infect. Dis.* **4**, ofx247 (2017).
- Bustos Carrillo, F., Gordon, A. & Harris E. Reply to Gerardin et al. *Clin. Infect. Dis.* **68**, 172–174 (2019).
- Ramon-Pardo, P., Cibrelus, L. & Yactayo, S., group, a. t. c. e. Chikungunya: case definitions for acute, atypical and chronic cases. Conclusions of an expert consultation, Managua, Nicaragua, 20–21 May 2015. *Wkly. Epidemiol. Rec.* **90**, 410–414 (2015).
- Godaert, L. et al. Atypical clinical presentations of acute phase chikungunya virus infection in older adults. *J. Am. Geriatr. Soc.* **65**, 2510–2515 (2017).
- Simon, F. et al. French guidelines for the management of chikungunya (acute and persistent presentations). November 2014. *Med. Mal. Infect.* **45**, 243–263 (2015).
- Zaid, A. et al. Chikungunya arthritis: implications of acute and chronic inflammation mechanisms on disease management. *Arthritis Rheumatol.* **70**, 484–495 (2018).

32. Teo, T. H. et al. Caribbean and La Réunion chikungunya virus isolates differ in their capacity to induce proinflammatory Th1 and NK cell responses and acute joint pathology. *J. Virol.* **89**, 7955–7969 (2015).
33. Langsjoen, R. M. et al. Chikungunya virus strains show lineage-specific variations in virulence and cross-protective ability in murine and nonhuman primate models. *MBio*. **9**, 1–13 (2018).
34. Acosta-Ampudia, Y. et al. Mayaro: an emerging viral threat? *Emerg. Microbes Infect.* **7**, 163 (2018).
35. Sales, G. et al. Treatment of chikungunya chronic arthritis: a systematic review. *Rev. Assoc. Med. Bras.* (1992) **64**, 63–70 (2018).
36. Prow, N. A. et al. Lower temperatures reduce type I interferon activity and promote alphavirus arthritis. *PLOS Pathog.* **13**, e1006788 (2017).
37. Runowska, M., Majewski, D., Niklas, K. & Puszczewicz, M. Chikungunya virus: a rheumatologist's perspective. *Clin. Exp. Rheumatol.* **36**, 494–501 (2018).
38. Economopoulou, A. et al. Atypical Chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005–2006 outbreak on Réunion. *Epidemiol. Infect.* **137**, 534–541 (2009).
39. Marques, C. D. L. et al. Recommendations of the Brazilian Society of Rheumatology for diagnosis and treatment of Chikungunya fever. Part 1 – Diagnosis and special situations. *Rev. Bras. Reumatol. Engl. Ed.* **57**, 421–437 (2017).
40. Silva, L. A. & Dermody, T. S. Chikungunya virus: epidemiology, replication, disease mechanisms, and prospective intervention strategies. *J. Clin. Invest.* **127**, 737–749 (2017).
41. Alvarez, M. F., Bolívar-Mejía, A., Rodríguez-Morales, A. J. & Ramírez-Vallejo, E. Cardiovascular involvement and manifestations of systemic Chikungunya virus infection: a systematic review. *F1000Res* **6**, 390 (2017).
42. Rolle, A. et al. Severe sepsis and septic shock associated with chikungunya virus infection, Guadeloupe, 2014. *Emerg. Infect. Dis.* **22**, 891–894 (2016).
43. Mehta, R. et al. The neurological complications of chikungunya virus: a systematic review. *Rev. Med. Virol.* **28**, e1978 (2018).
44. Gerardin, P. et al. Chikungunya virus-associated encephalitis: a cohort study on La Réunion Island, 2005–2009. *Neurology* **86**, 94–102 (2016).
45. Mercado, M. et al. Renal involvement in fatal cases of chikungunya virus infection. *J. Clin. Virol.* **103**, 16–18 (2018).
46. Chopra, A., Anuradha, V., Ghorpade, R. & Saluja, M. Acute Chikungunya and persistent musculoskeletal pain following the 2006 Indian epidemic: a 2-year prospective rural community study. *Epidemiol. Infect.* **140**, 842–850 (2012).
47. Couderc, T. & Lecuit, M. Chikungunya virus pathogenesis: from bedside to bench. *Antiviral Res.* **121**, 120–131 (2015).
48. Mylonas, A. D. et al. Natural history of Ross River virus-induced epidemic polyarthritis. *Med. J. Aust.* **177**, 356–360 (2002).
49. Briggs, A. M. et al. Reducing the global burden of musculoskeletal conditions. *Bull. World Health Organ.* **96**, 366–368 (2018).
50. Ritz, N., Hufnagel, M. & Cerardin, P. Chikungunya in children. *Pediatr. Infect. Dis. J.* **34**, 789–791 (2015).
51. Pinzon-Redondo, H. et al. Risk factors for severity of chikungunya in children: a prospective assessment. *Pediatr. Infect. Dis. J.* **35**, 702–704 (2016).
52. Chandorkar, N., Raj, D., Kumar, R. & Warsi, S. Fever, marked tachycardia and vesiculobullous rash in an infant with Chikungunya fever. *BMJ Case Rep.* **2017**, bcr-2016-218687 (2017).
53. Dubrocq, G., Wang, K., Spaeder, M. C. & Hahn, A. Septic shock secondary to chikungunya virus in a 3-month-old traveler returning from Honduras. *J. Pediatr. Infect. Dis. Soc.* **6**, e158–e160 (2017).
54. Robin, S. et al. Neurologic manifestations of pediatric chikungunya infection. *J. Child Neurol.* **23**, 1028–1035 (2008).
55. Simarmata, D. et al. Early clearance of Chikungunya virus in children is associated with a strong innate immune response. *Sci. Rep.* **6**, 26097 (2016).
56. Gordon, A. et al. Differences in transmission and disease severity between two successive waves of chikungunya. *Clin. Infect. Dis.* **67**, 1760–1767 (2018).
57. Kumar, A., Best, C. & Benskin, G. Epidemiology, clinical and laboratory features and course of chikungunya among a cohort of children during the first caribbean epidemic. *J. Trop. Pediatr.* **63**, 43–49 (2017).
58. Samra, J. A., Hagood, N. L., Summer, A., Medina, M. T. & Holden, K. R. Clinical features and neurologic complications of children hospitalized with chikungunya virus in Honduras. *J. Child Neurol.* **32**, 712–716 (2017).
59. Sharma, P. K. et al. Severe manifestations of chikungunya fever in children, India, 2016. *Emerg. Infect. Dis.* **24**, 1737–1739 (2018).
60. Badawi, A., Ryoo, S. G., Vasileva, D. & Yaghoubi, S. Prevalence of chronic comorbidities in chikungunya: a systematic review and meta-analysis. *Int. J. Infect. Dis.* **67**, 107–113 (2018).
61. De Almeida Barreto, F. K. et al. Chikungunya and diabetes, what do we know? *Diabetology & Metabolic Syndrome* **10**, 32 (2018).
62. Crosby, L. et al. Severe manifestations of chikungunya virus in critically ill patients during the 2013–2014 Caribbean outbreak. *Int. J. Infect. Dis.* **48**, 78–80 (2016).
63. Koeltz, A., Lastere, S. & Jean-Baptiste, S. Intensive care admissions for severe chikungunya virus infection, French Polynesia. *Emerg. Infect. Dis.* **24**, 794–796 (2018).
64. Rosso, F. et al. Chikungunya in solid organ transplant recipients, a case series and literature review. *Transpl. Infect. Dis.* **20**, e12978 (2018).
65. Salam, N. et al. Global prevalence and distribution of coinfection of malaria, dengue and chikungunya: a systematic review. *BMC Public Health* **18**, 710 (2018).
66. Campos, M. C. et al. Zika might not be acting alone: using an ecological study approach to investigate potential co-acting risk factors for an unusual pattern of microcephaly in Brazil. *PLOS ONE* **13**, e0201452 (2018).
67. Carrillo-Hernandez, M. Y., Ruiz-Saenz, J., Villamizar, L. J., Gomez-Rangel, S. Y. & Martinez-Gutierrez, M. Co-circulation and simultaneous co-infection of dengue, chikungunya, and Zika viruses in patients with febrile syndrome at the Colombian–Venezuelan border. *BMC Infect. Dis.* **18**, 61 (2018).
68. Waggoner, J. J. et al. Viremia and clinical presentation in Nicaraguan patients infected with Zika virus, chikungunya virus, and dengue virus. *Clin. Infect. Dis.* **63**, 1584–1590 (2016).
69. Taraphdar, D., Sarkar, A., Mukhopadhyay, B. B. & Chatterjee, S. A comparative study of clinical features between monotypic and dual infection cases with Chikungunya virus and dengue virus in West Bengal, India. *Am. J. Trop. Med. Hyg.* **86**, 720–723 (2012).
70. Londhey, V. et al. Dengue and chikungunya virus co-infections: the inside story. *J. Assoc. Physicians India* **64**, 36–40 (2016).
71. Edwards, T. et al. Co-infections with chikungunya and dengue viruses, Guatemala, 2015. *Emerg. Infect. Dis.* **22**, 2003–2005 (2016).
72. Mercado, M. et al. Clinical and histopathological features of fatal cases with dengue and chikungunya virus co-infection in Colombia, 2014 to 2015. *Euro. Surveill.* <https://doi.org/10.2807/1560-7917.ES.2016.21.22.30244> (2016).
73. Gandhi, B. S. et al. Dengue and Chikungunya co-infection associated with more severe clinical disease than mono-infection. *Int. J. Healthcare Biomed. Res.* **03**, 117–123 (2015).
74. Elsinga, J., Halabi, Y., Gerstenbluth, I., Tami, A. & Grobusch, M. P. Consequences of a recent past dengue infection for acute and long-term chikungunya outcome: a retrospective cohort study in Curacao. *Travel Med. Infect. Dis.* **23**, 34–43 (2018).
75. Singh, J. et al. Clinical profile of dengue fever and coinfection with chikungunya. *Ci Ji Yi Xue Za Zhi* **30**, 158–164 (2018).
76. Villamil-Gómez, W. E. et al. Dengue, chikungunya and Zika coinfection in a patient from Colombia. *J. Infect. Public Health* **9**, 684–686 (2016).
77. Vogels, C. B. F. et al. Arbovirus coinfection and co-transmission: a neglected public health concern? *PLOS Biol* **17**, e3000130 (2019).
78. Centers for disease control and prevention. CHIKUNGUNYA Clinical management in dengue-endemic areas. https://www.cdc.gov/chikungunya/pdfs/CHIKV_DengueEndemic.pdf (2014).
79. Hertz, J. T. et al. Chikungunya and dengue fever among hospitalized febrile patients in northern Tanzania. *Am. J. Trop. Med. Hyg.* **86**, 171–177 (2012).
80. Teo, T. H. et al. Plasmodium co-infection protects against chikungunya virus-induced pathologies. *Nat. Commun.* **9**, 3905 (2018).
81. McCarthy, M. K. et al. Chikungunya virus impairs draining lymph node function by inhibiting HEV-mediated lymphocyte recruitment. *JCI Insight* **3**, e121100 (2018).
82. Teo, T. H. et al. Co-infection with Chikungunya virus alters trafficking of pathogenic CD8⁺ T cells into the brain and prevents plasmodium-induced neuropathology. *EMBO Mol. Med.* **10**, 121–138 (2018).
83. Ng, L. F. P. Immunopathology of chikungunya virus infection: lessons learned from patients and animal models. *Annu. Rev. Virol.* **4**, 413–427 (2017).
84. Haese, N. N. et al. Animal models of chikungunya virus infection and disease. *J. Infect. Dis.* **214**, S482–S487 (2016).
85. Fox, J. M. & Diamond, M. S. Immune-mediated protection and pathogenesis of chikungunya virus. *J. Immunol.* **197**, 4210–4218 (2016).
86. Baxter, V. K. & Heise, M. T. Genetic control of alphavirus pathogenesis. *Mamm. Genome* **29**, 408–424 (2018).
87. Mathew, A. J. et al. Chikungunya infection: a global public health menace. *Curr. Allergy Asthma Rep.* **17**, 13 (2017).
88. Carpentier, K. S. & Morrison, T. E. Innate immune control of alphavirus infection. *Curr. Opin. Virol.* **28**, 53–60 (2018).
89. Rudd, P. A. et al. Interferon response factors 3 and 7 protect against Chikungunya virus hemorrhagic fever and shock. *J. Virol.* **86**, 9888–9898 (2012).
90. Wilson, J. A. et al. RNA-Seq analysis of chikungunya virus infection and identification of granzyme A as a major promoter of arthritic inflammation. *PLOS Pathog.* **13**, e1006155 (2017).
91. Poo, Y. S. et al. Multiple immune factors are involved in controlling acute and chronic chikungunya virus infection. *PLOS Negl. Trop. Dis.* **8**, e3354 (2014).
92. Molony, R. D. et al. Aging impairs both primary and secondary RIG-I signaling for interferon induction in human monocytes. *Sci. Signal* **10**, 1–26 (2017).
93. Molony, R. D., Malawista, A. & Montgomery, R. R. Reduced dynamic range of antiviral innate immune responses in aging. *Exp. Gerontol.* **107**, 130–135 (2018).
94. Marr, N. et al. Attenuation of respiratory syncytial virus-induced and RIG-I-dependent type I IFN responses in human neonates and very young children. *J. Immunol.* **192**, 948–957 (2014).
95. Danis, B. et al. Interferon regulatory factor 7-mediated responses are defective in cord blood plasmacytoid dendritic cells. *Eur. J. Immunol.* **38**, 507–517 (2008).
96. Lu, S. H., Leasure, A. R. & Dai, Y. T. A systematic review of body temperature variations in older people. *J. Clin. Nurs.* **19**, 4–16 (2010).
97. Gunes, U. Y. & Zaybak, A. Does the body temperature change in older people? *J. Clin. Nurs.* **17**, 2284–2287 (2008).
98. Yoon, I. K. et al. High rate of subclinical chikungunya virus infection and association of neutralizing antibody with protection in a prospective cohort in the Philippines. *PLOS Negl. Trop. Dis.* **9**, e0003764 (2015).
99. Chua, C. L., Sam, I. C., Chiam, C. W. & Chan, Y. F. The neutralizing role of IgM during early Chikungunya virus infection. *PLOS ONE* **12**, e0171989 (2017).
100. Kam, Y. W. et al. Early appearance of neutralizing immunoglobulin G3 antibodies is associated with chikungunya virus clearance and long-term clinical protection. *J. Infect. Dis.* **205**, 1147–1154 (2012).
101. Gardner, J. et al. Chikungunya virus arthritis in adult wild-type mice. *J. Virol.* **84**, 8021–8032 (2010).
102. Haist, K. C., Burrack, K. S., Davenport, B. J. & Morrison, T. E. Inflammatory monocytes mediate control of acute alphavirus infection in mice. *PLOS Pathog.* **13**, e1006748 (2017).
103. Fox, J. M. et al. Optimal therapeutic activity of monoclonal antibodies against chikungunya virus requires FcγR interaction on monocytes. *Sci. Immunol.* **4**, 1–13 (2019).
104. Poo, Y. S. et al. CCR2 deficiency promotes exacerbated chronic erosive neutrophil-dominated chikungunya virus arthritis. *J. Virol.* **88**, 6862–6872 (2014).
105. Ikeda, N. et al. Emergence of immunoregulatory Ym1⁺Ly6C⁺ monocytes during recovery phase of tissue injury. *Sci. Immunol.* **3**, eaat0207 (2018).
106. Long, K. M. & Heise, M. T. Protective and pathogenic responses to chikungunya virus infection. *Curr. Trop. Med. Rep.* **2**, 13–21 (2015).
107. Thanapati, S. T. et al. Impaired NK cell functionality and increased TNF-α production as biomarkers of chronic chikungunya arthritis and rheumatoid arthritis. *Hum. Immunol.* **78**, 370–374 (2017).
108. Michlmayr, D. et al. Comprehensive innate immune profiling of chikungunya virus infection in pediatric cases. *Mol. Syst. Biol.* **14**, e7862 (2018).
109. Labadie, K. et al. Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages. *J. Clin. Invest.* **120**, 894–906 (2010).

110. Blettery, M. et al. Brief report: management of chronic post-chikungunya rheumatic disease: the Martinican experience. *Arthritis Rheumatol.* **68**, 2817–2824 (2016).
111. Zaid, A., Rulli, N. E., Rolph, M. S., Suhrbier, A. & Mahalingam, S. Disease exacerbation by etanercept in a mouse model of alphaviral arthritis and myositis. *Arthritis Rheum.* **63**, 488–491 (2011).
112. Hoarau, J. J. et al. Persistent chronic inflammation and infection by Chikungunya arthritogenic alphavirus in spite of a robust host immune response. *J. Immunol.* **184**, 5914–5927 (2010).
113. Guaraldo, L. et al. Treatment of chikungunya musculoskeletal disorders: a systematic review. *Expert Rev. Anti Infect. Ther.* **16**, 333–344 (2018).
114. Soden, M. et al. Detection of viral ribonucleic acid and histologic analysis of inflamed synovium in Ross River virus infection. *Arthritis Rheum.* **43**, 365–369 (2000).
115. Hazeltin, R. A., Hughes, C. & Askov, J. G. The inflammatory response in the synovium of a patient with Ross River arbovirus infection. *Aust. N. Z. J. Med.* **15**, 336–339 (1985).
116. Fraser, J. R., Cunningham, A. L., Clariss, B. J., Askov, J. G. & Leach, R. Cytology of synovial effusions in epidemic polyarthritis. *Aust. N. Z. J. Med.* **11**, 168–173 (1981).
117. Suhrbier, A. & Mahalingam, S. The immunobiology of viral arthritides. *Pharmacol. Ther.* **124**, 301–308 (2009).
118. Dupuis-Maguiraga, L. et al. Chikungunya disease: infection-associated markers from the acute to the chronic phase of arbovirus-induced arthralgia. *PLOS Negl. Trop. Dis.* **6**, e1446 (2012).
119. Schwartz, O. & Albert, M. L. Biology and pathogenesis of chikungunya virus. *Nat. Rev. Microbiol.* **8**, 491–500 (2010).
120. Zhang, R. et al. Mxra8 is a receptor for multiple arthritogenic alphaviruses. *Nature* **557**, 570–574 (2018).
121. Akhrymuk, I., Lukash, T., Frolov, I. & Frolova, E. I. Novel mutations in nsP2 abolish chikungunya virus-induced transcriptional shutoff and make the virus less cytopathic without affecting its replication rates. *J. Virol.* **93**, e02062–18 (2019).
122. Lim, S. M. et al. Transcriptomic analyses reveal differential gene expression of immune and cell death pathways in the brains of mice infected with West Nile virus and chikungunya virus. *Front. Microbiol.* **8**, 1556 (2017).
123. Das, T., Hoarau, J. J., Jaffar Bandjee, M. C., Maquart, M. & Gasque, P. Multifaceted innate immune responses engaged by astrocytes, microglia and resident dendritic cells against Chikungunya neuroinfection. *J. Gen. Virol.* **96**, 294–310 (2015).
124. Fraser, J. R. & Becker, G. J. Mononuclear cell types in chronic synovial effusions of Ross River virus disease. *Aust. N. Z. J. Med.* **14**, 505–506 (1984).
125. Suhrbier, A. & La Linn, M. Clinical and pathologic aspects of arthritis due to Ross River virus and other alphaviruses. *Curr. Opin. Rheumatol.* **16**, 374–379 (2004).
126. Nayak, T. K. et al. P38 and Jnk mitogen-activated protein kinases interact with chikungunya virus non-structural protein-2 and regulate TNF induction during viral infection in macrophages. *Front. Immunol.* **10**, 786 (2019).
127. Chen, W. et al. Specific inhibition of NLRP3 in chikungunya disease reveals a role for inflammasomes in alphavirus-induced inflammation. *Nat. Microbiol.* **2**, 1435–1445 (2017).
128. Guo, C. et al. NLRP3 inflammasome activation contributes to the pathogenesis of rheumatoid arthritis. *Clin. Exp. Immunol.* **194**, 231–243 (2018).
129. Ruiz Silva, M., Van der Ende-Metselaar, H., Mulder, H. L., Smit, J. M. & Rodenhuis-Zybert, I. A. Mechanism and role of MCP-1 upregulation upon chikungunya virus infection in human peripheral blood mononuclear cells. *Sci. Rep.* **6**, 32288 (2016).
130. Her, Z. et al. Active infection of human blood monocytes by Chikungunya virus triggers an innate immune response. *J. Immunol.* **184**, 5903–5913 (2010).
131. Shapouri-Moghaddam, A. et al. Macrophage plasticity, polarization, and function in health and disease. *J. Cell Physiol.* **233**, 6425–6440 (2018).
132. Nakaya, H. I. et al. Gene profiling of Chikungunya virus arthritis in a mouse model reveals significant overlap with rheumatoid arthritis. *Arthritis Rheum.* **64**, 3553–3563 (2012).
133. Teo, T. H. et al. Fingolimod treatment abrogates chikungunya virus-induced arthralgia. *Sci. Transl. Med.* **9**, 1–11 (2017).
134. Kulkarni, S. P. et al. Regulatory T cells and IL-10 as modulators of chikungunya disease outcome: a preliminary study. *Eur. J. Clin. Microbiol. Infect. Dis.* **36**, 2475–2481 (2017).
135. Carissimo, G. et al. Viperin controls chikungunya virus-specific pathogenic T cell IFN γ Th1 stimulation in mice. *Life Sci. Alliance* **2**, 1–13 (2019).
136. Miner, J. J. et al. Therapy with CTLA4-Ig and an antiviral monoclonal antibody controls chikungunya virus arthritis. *Sci. Transl. Med.* **9**, eaah3438 (2017).
137. Lee, W. W. et al. Expanding regulatory T cells alleviates chikungunya virus-induced pathology in mice. *J. Virol.* **89**, 7893–7904 (2015).
138. Teo, T. H. et al. A pathogenic role for CD4 $^{+}$ T cells during Chikungunya virus infection in mice. *J. Immunol.* **190**, 259–269 (2013).
139. Nehmar, R. et al. Therapeutic perspectives for interferons and plasmacytoid dendritic cells in rheumatoid arthritis. *Trends Mol. Med.* **24**, 338–347 (2018).
140. Karonitsch, T. et al. Targeted inhibition of Janus kinases abates interferon- γ -induced invasive behaviour of fibroblast-like synoviocytes. *Rheumatology* **57**, 572–577 (2018).
141. Roberts, C. A., Dickinson, A. K. & Taams, L. S. The interplay between monocytes/macrophages and CD4 $^{+}$ T cell subsets in rheumatoid arthritis. *Front. Immunol.* **6**, 571 (2015).
142. Parker, D. CD80/CD86 signaling contributes to the proinflammatory response of *Staphylococcus aureus* in the airway. *Cytokine* **107**, 130–136 (2018).
143. Wade, S. M. et al. Association of synovial tissue polyfunctional T-cells with DAPSA in psoriatic arthritis. *Ann. Rheum. Dis.* **78**, 350–354 (2019).
144. Rudwaleit, M. et al. Response to methotrexate in early rheumatoid arthritis is associated with a decrease of T cell derived tumour necrosis factor α , increase of interleukin 10, and predicted by the initial concentration of interleukin 4. *Ann. Rheum. Dis.* **59**, 311–314 (2000).
145. Haroon, N., Srivastava, R., Misra, R. & Aggarwal, A. A novel predictor of clinical response to methotrexate in patients with rheumatoid arthritis: a pilot study of in vitro T cell cytokine suppression. *J. Rheumatol.* **35**, 975–978 (2008).
146. Monge, P. et al. Pan-American League of Associations for Rheumatology – Central American, Caribbean and Andean Rheumatology Association Consensus – Conference endorsements and recommendations on the diagnosis and treatment of chikungunya-related inflammatory arthropathies in Latin America. *J. Clin. Rheumatol.* **25**, 101–107 (2018).
147. Bedoui, Y. et al. Immunomodulatory drug methotrexate used to treat patients with chronic inflammatory rheumatism post-chikungunya does not impair the synovial antiviral and bone repair responses. *PLOS Negl. Trop. Dis.* **12**, e0006634 (2018).
148. Chen, W. et al. Arthritogenic alphaviruses: new insights into arthritis and bone pathology. *Trends Microbiol.* **23**, 35–43 (2015).
149. Ng, L. F. et al. IL-1 β , IL-6, and RANTES as biomarkers of Chikungunya severity. *PLOS ONE* **4**, e4261 (2009).
150. Chow, A. et al. Persistent arthralgia induced by Chikungunya virus infection is associated with interleukin-6 and granulocyte macrophage colony-stimulating factor. *J. Infect. Dis.* **203**, 149–157 (2011).
151. Robert, M. & Miossec, P. IL-17 in rheumatoid arthritis and precision medicine: from synovitis expression to circulating bioactive levels. *Front. Med.* **5**, 364 (2019).
152. Lokireddy, S., Vemula, S. & Vadde, R. Connective tissue metabolism in chikungunya patients. *Virol. J.* **5**, 31 (2008).
153. Maucourant, C., Petitdemange, C., Yssel, H. & Vieillard, V. Control of acute arboviral infection by natural killer cells. *Viruses* **11**, E131 (2019).
154. Yamin, R. K. et al. High percentages and activity of synovial fluid NK cells present in patients with advanced stage active rheumatoid arthritis. *Sci. Rep.* **9**, 1351 (2019).
155. Phuklia, W. et al. Osteoclastogenesis induced by CHIKV-infected fibroblast-like synoviocytes: a possible interplay between synoviocytes and monocytes/macrophages in CHIKV-induced arthralgia/arthritis. *Virus Res.* **177**, 179–188 (2013).
156. Sukkaew, A. et al. Heterogeneity of clinical isolates of chikungunya virus and its impact on the responses of primary human fibroblast-like synoviocytes. *J. Gen. Virol.* **99**, 525–535 (2018).
157. Noret, M. et al. Interleukin 6, RANKL, and osteoprotegerin expression by chikungunya virus-infected human osteoblasts. *J. Infect. Dis.* **206**, 455–457 (2012).
158. Chen, W. et al. Arthritogenic alphaviral infection perturbs osteoblast function and triggers pathologic bone loss. *Proc. Natl. Acad. Sci. U. S. A.* **111**, 6040–6045 (2014).
159. Kuo, S. C. et al. Suramin treatment reduces chikungunya pathogenesis in mice. *Antiviral Res.* **134**, 89–96 (2016).
160. Lim, E. X. Y. et al. Chondrocytes contribute to alphaviral disease pathogenesis as a source of virus replication and soluble factor production. *Viruses* **10**, E86 (2018).
161. Ozden, S. et al. Human muscle satellite cells as targets of Chikungunya virus infection. *PLOS ONE* **2**, e527 (2007).
162. Kawane, K. et al. Chronic polyarthritis caused by mammalian DNA that escapes from degradation in macrophages. *Nature* **443**, 998–1002 (2006).
163. Nikitina, E., Larionova, I., Choinzonov, E. & Kzhyshkowska, J. Monocytes and macrophages as viral targets and reservoirs. *Int. J. Mol. Sci.* **19**, 1–25 (2018).
164. Krejbich-Trotot, P. et al. Chikungunya virus mobilizes the apoptotic machinery to invade host cell defenses. *FASEB J.* **25**, 314–325 (2011).
165. Remenyi, R. et al. Persistent replication of a chikungunya virus replicon in human cells is associated with presence of stable cytoplasmic granules containing nonstructural protein 3. *J. Virol.* **92**, 1–24 (2018).
166. Chang, A. Y. et al. Frequency of chronic joint pain following chikungunya virus infection: a colombian cohort study. *Arthritis Rheumatol.* **70**, 578–584 (2018).
167. Cook, A. D., Christensen, A. D., Tewari, D., McMahon, S. B. & Hamilton, J. A. Immune cytokines and their receptors in inflammatory pain. *Trends Immunol.* **39**, 240–255 (2018).
168. Choy, E. H. S. & Calabrese, L. H. Neuroendocrine and neurophysiological effects of interleukin 6 in rheumatoid arthritis. *Rheumatology* **57**, 1885–1895 (2018).
169. Brito, C. A. et al. Pharmacologic management of pain in patients with Chikungunya: a guideline. *Rev. Soc. Bras. Med. Trop.* **49**, 668–679 (2016).
170. de Andrade, D. C., Jean, S., Clavelou, P., Dallel, R. & Bouhassira, D. Chronic pain associated with the Chikungunya Fever: long lasting burden of an acute illness. *BMC Infect. Dis.* **10**, 31 (2010).
171. Marques, C. D. L. et al. Recommendations of the Brazilian Society of Rheumatology for the diagnosis and treatment of chikungunya fever. II. Treatment. *Rev. Bras. Reumatol. Engl. Ed.* **57**, 438–451 (2017).
172. Sutarra, R. B., Amaral, J. K. & Schoen, R. T. Emergence and treatment of chikungunya arthritis. *Curr. Opin. Rheumatol.* **30**, 256–263 (2018).
173. Marti-Carvajal, A. et al. Interventions for treating patients with chikungunya virus infection-related rheumatic and musculoskeletal disorders: a systematic review. *PLOS ONE* **12**, e0179028 (2017).
174. Cunha, R. V. D. & Trinta, K. S. Chikungunya virus: clinical aspects and treatment – a review. *Mem. Inst. Oswaldo Cruz* **112**, 523–531 (2017).
175. Sharma, S. K. & Jain, S. Chikungunya: a rheumatologist's perspective. *Int. J. Rheum. Dis.* **21**, 584–601 (2018).
176. Mylonas, A. D. et al. Corticosteroid therapy in an alphaviral arthritis. *J. Clin. Rheumatol.* **10**, 326–330 (2004).
177. Taylor, A. et al. Methotrexate treatment causes early onset of disease in a mouse model of Ross River virus-induced inflammatory disease through increased monocyte production. *PLOS ONE* **8**, e71146 (2013).
178. Roques, P. et al. Paradoxical effect of chloroquine treatment in enhancing chikungunya virus infection. *Viruses* **10**, E268 (2018).
179. Ziemssen, T. et al. Real-world persistence and benefit-risk profile of fingolimod over 36 months in Germany. *Neurol. Neuroimmunol. Neuroinflamm.* **6**, e548 (2019).
180. Jin, J. et al. Neutralizing antibodies inhibit chikungunya virus budding at the plasma membrane. *Cell Host Microbe* **24**, 417–428 e415 (2018).
181. Goh, L. Y. et al. Neutralizing monoclonal antibodies to the E2 protein of chikungunya virus protects against disease in a mouse model. *Clin. Immunol.* **149**, 487–497 (2013).
182. Prow, N. A. et al. A vaccinia-based single vector construct multi-pathogen vaccine protects against both Zika and chikungunya viruses. *Nat. Commun.* **9**, 1230 (2018).
183. Powers, A. M. Vaccine and therapeutic options to control chikungunya virus. *Clin. Microbiol. Rev.* **31**, e00104–e00116 (2018).
184. Jin, J. et al. Neutralizing monoclonal antibodies block chikungunya virus entry and release by targeting an epitope critical to viral pathogenesis. *Cell Rep.* **13**, 2553–2564 (2015).
185. Research and markets. Global Influenza Vaccine Market Report 2018-2024 Featuring Seqirus,

- GlaxoSmithKline., Sanofi Pasteur., Novavax, & Emergent BioSolutions. *CISION PR Newswire* <https://www.prnewswire.com/news-releases/global-influenza-vaccine-market-report-2018-2024-featuring-seqirus-glaxosmithkline-sanofi-pasteur-novavax-emergent-biosolutions-300824955.html> (2019)
186. Kang, G. Chikungunya vaccines in the pipeline. Presented at the Workshop on Chikungunya vaccines, Delhi http://www.who.int/immunization/research/meetings_workshops/28_Kang_Chikungunya.pdf (2018).
187. US National Library of Medicine. ClinicalTrials.gov <https://clinicaltrials.gov/ct2/show/NCT02861586> (2018).
188. US National Library of Medicine. ClinicalTrials.gov <https://clinicaltrials.gov/show/NCT02562482> (2019).
189. Butler, D. Health officials push for vaccine against neglected tropical virus. *Nature* <https://www.nature.com/articles/d41586-018-01637-7> (2018).
190. Kirkpatrick, B. D. et al. The live attenuated dengue vaccine TV003 elicits complete protection against dengue in a human challenge model. *Sci. Transl. Med.* **8**, 330ra336 (2016).
191. Roques, P. et al. Attenuated and vectored vaccines protect nonhuman primates against Chikungunya virus. *JCI Insight* **2**, e83527 (2017).
192. Milligan, G. N., Schnierle, B. S., McAuley, A. J. & Beasley, D. W. C. Defining a correlate of protection for chikungunya virus vaccines. *Vaccine* <https://doi.org/10.1016/j.vaccine.2018.10.033> (2018).
193. Prow, N. A., Jimenez Martinez, R., Hayball, J. D., Howley, P. M. & Suhrbier, A. Poxvirus-based vector systems and the potential for multi-valent and multi-pathogen vaccines. *Expert Rev. Vaccines* **17**, 925–934 (2018).
194. Auerswald, H. et al. Broad and long-lasting immune protection against various Chikungunya genotypes demonstrated by participants in a cross-sectional study in a Cambodian rural community. *Emerg. Microbes Infect.* **7**, 13 (2018).
195. Goo, L. et al. A virus-like particle vaccine elicits broad neutralizing antibody responses in humans to all chikungunya virus genotypes. *J. Infect. Dis.* **214**, 1487–1491 (2016).
196. Chua, C. L., Sam, I. C., Merits, A. & Chan, Y. F. Antigenic variation of East/Central/South African and Asian chikungunya virus genotypes in neutralization by immune sera. *PLOS Negl. Trop. Dis.* **10**, e0004960 (2016).
197. Gerardin, P. et al. Estimating Chikungunya prevalence in La Réunion Island outbreak by serosurveys: two methods for two critical times of the epidemic. *BMC Infect. Dis.* **8**, 99 (2008).
198. Shanks, G. D. Could Ross River virus be the next Zika? *J. Travel Med.* **26**, taz003 (2019).
199. Borgherini, G. et al. Outbreak of chikungunya on Réunion Island: early clinical and laboratory features in 157 adult patients. *Clin. Infect. Dis.* **44**, 1401–1407 (2007).
200. Peters, C. M. M. et al. Chikungunya virus outbreak in Sint Maarten: long-term arthralgia after a 15-month period. *J. Vector Borne Dis.* **55**, 137–143 (2018).
201. Jain, J. et al. Clinical, serological, and virological analysis of 572 chikungunya patients from 2010 to 2013 in India. *Clin. Infect. Dis.* **65**, 133–140 (2017).
202. Schilte, C. et al. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study. *PLOS Negl. Trop. Dis.* **7**, e2137 (2013).
203. Amaral, J. K., Taylor, P. C., Teixeira, M. M., Morrison, T. E. T. & Schoen, R. T. The clinical features, pathogenesis and methotrexate therapy of chronic chikungunya arthritis. *Viruses* **11**, 289 (2019).
204. Chang, A. Y. et al. Chikungunya arthritis mechanisms in the Americas: a cross-sectional analysis of chikungunya arthritis patients twenty-two months after infection demonstrating no detectable viral persistence in synovial fluid. *Arthritis Rheumatol.* **70**, 585–593 (2018).
205. Heath, C. J. et al. The identification of risk factors for chronic chikungunya arthralgia in Grenada, West Indies: a cross-sectional cohort study. *Open Forum Infect. Dis.* **5**, ofx234 (2018).
206. Huits, R. et al. Chikungunya virus infection in Aruba: diagnosis, clinical features and predictors of post-chikungunya chronic polyarthralgia. *PLOS ONE* **13**, e0196630 (2018).
207. Queyriaux, B. et al. Clinical burden of chikungunya virus infection. *Lancet Infect. Dis.* **8**, 2–3 (2008).
208. Aly, M. M. et al. Severe chikungunya infection in Northern Mozambique: a case report. *BMC Res. Notes* **10**, 88 (2017).
209. Gardner, J. et al. Infectious chikungunya virus in the saliva of mice, monkeys and humans. *PLOS ONE* **10**, e0139481 (2015).
210. Mahendradas, P., Avadhani, K. & Shetty, R. Chikungunya and the eye: a review. *J. Ophthalmic Inflamm. Infect.* **3**, 35 (2013).
211. Ulloa-Padilla, J. P., Davila, P. J., Izquierdo, N. J., Garcia-Rodriguez, O. & Jimenez, I. Z. Ocular symptoms and signs of chikungunya fever in puerto rico. *P. R. Health Sci. J.* **37**, 83–87 (2018).
212. Drame, M. et al. Clinical forms of chikungunya virus infection: the challenge and utility of a consensus definition. *Am. J. Trop. Med. Hyg.* **99**, 552–553 (2018).
213. Azeredo, E. L. et al. Clinical and laboratory profile of Zika and dengue infected patients: lessons learned from the co-circulation of dengue, Zika and chikungunya in Brazil. *PLOS Curr* **10**, <https://doi.org/10.1371/currents.outbreaks.0bf6aeb4d30824de63c4d5d745b2175> (2018).
214. World Health Organization. Guidelines for prevention and control of chikungunya fever. *World Health Organization* <http://apps.who.int/iris/bitstream/handle/10665/205166/B4289.pdf> (2009).
215. Contopoulos-Ioannidis, D., Newman-Lindsay, S., Chow, C. & LaBeaud, A. D. Mother-to-child transmission of Chikungunya virus: a systematic review and meta-analysis. *PLOS Negl. Trop. Dis.* **12**, e0006510 (2018).
216. Villamil-Gomez, W. et al. Congenital chikungunya virus infection in Sincelejo, Colombia: a case series. *J. Trop. Pediatr.* **61**, 386–392 (2015).
217. Gerardin, P. et al. Multidisciplinary prospective study of mother-to-child chikungunya virus infections on the island of La Réunion. *PLOS Med* **5**, e60 (2008).
218. Torres, J. R. et al. Congenital and perinatal complications of chikungunya fever: a Latin American experience. *Int. J. Infect. Dis.* **51**, 85–88 (2016).
219. Lyra, P. P. et al. Congenital chikungunya virus infection after an outbreak in Salvador, Bahia, Brazil. *AJP Rep.* **6**, e299–e300 (2016).
220. Gerardin, P. et al. Neurocognitive outcome of children exposed to perinatal mother-to-child Chikungunya virus infection: the CHIMERE cohort study on Réunion Island. *PLOS Negl. Trop. Dis.* **8**, e2996 (2014).
221. US National Library of Medicine. ClinicalTrials.gov <https://clinicaltrials.gov/show/NCT02230163> (2014).
222. Hanley, M. et al. Tocolysis: a review of the literature. *Obstet. Gynecol. Surv.* **74**, 50–55 (2019).
223. Bolden, J. R. Acute and chronic tocolysis. *Clin. Obstet. Gynecol.* **57**, 568–578 (2014).
224. Escobar, M. F., Mora, B. L., Cedano, J. A., Loaiza, S. & Rosso, F. Comprehensive treatment in severe dengue during preterm and term labor: could tocolysis be useful? *J. Matern. Fetal Neonatal Med.* **9**, 1–6 (2019).
225. Ramos, R. et al. Perinatal chikungunya virus-associated encephalitis leading to postnatal-onset microcephaly and optic atrophy. *Pediatr. Infect. Dis. J.* **37**, 94–95 (2018).
226. Matusali, G. et al. Tropism of the chikungunya virus. *Viruses* **11**, E175 (2019).
227. Fortuna, C. et al. Vector competence of *Aedes albopictus* for the Indian Ocean lineage (IOL) chikungunya viruses of the 2007 and 2017 outbreaks in Italy: a comparison between strains with and without the E1:A226V mutation. *Euro. Surveill.* **23**, 1800246 (2018).
228. Maynard, A. J. et al. Tiger on the prowl: invasion history and spatio-temporal genetic structure of the Asian tiger mosquito *Aedes albopictus* (Skuse 1894) in the Indo-Pacific. *PLOS Negl. Trop. Dis.* **11**, e0005546 (2017).
229. Shaw, W. R. & Catteruccia, F. Vector biology meets disease control: using basic research to fight vector-borne diseases. *Nat. Microbiol.* **4**, 20–34 (2018).
230. Feldstein, L. R., Rowhani-Rahbar, A., Staples, J. E., Halloran, M. E. & Ellis, E. M. An assessment of household and individual-level mosquito prevention methods during the chikungunya virus outbreak in the United States Virgin Islands, 2014–2015. *Am. J. Trop. Med. Hyg.* **98**, 845–848 (2018).
231. Roiz, D. et al. Integrated Aedes management for the control of Aedes-borne diseases. *PLOS Negl. Trop. Dis.* **12**, e0006845 (2018).
232. Lovett, B. et al. Transgenic *Metarhizium* rapidly kills mosquitoes in a malaria-endemic region of Burkina Faso. *Science* **364**, 894–897 (2019).
233. Anders, K. L. et al. The AWED trial (Applying Wolbachia to Eliminate Dengue) to assess the efficacy of Wolbachia-infected mosquito deployments to reduce dengue incidence in Yogyakarta, Indonesia: study protocol for a cluster randomised controlled trial. *Trials* **19**, 302 (2018).
234. O'Neill, S. L. et al. Scaled deployment of Wolbachia to protect the community from Aedes transmitted arboviruses. *Gates Open Res.* **2**, 1–24 (2018).

Acknowledgements

A.S. would like to thank Rocío Jimenez Martinez, Viviana Lutzky, Yee Suan Poo, Jillann F. Farmer, Patrick Gerardin and David Warrilow for their help with the preparation and review of various aspects of the article. A.S. is a Principal Research Fellow with the National Health and Medical Research Council of Australia.

Competing interests

A.S. declares that he is a consultant for Sementis Ltd., a company that is developing vaccines against chikungunya virus and Zika virus. A.S. declares that he has been a consultant for Valneva and GSK, which are also developing CHIKV vaccines.

Peer review information

Nature Reviews Rheumatology thanks R. Schoen, A.J. Rodriguez-Morales, and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary information

Supplementary information is available for this paper at <https://doi.org/10.1038/s41584-019-0276-9>.